CHAPTER

79 Cardiac Disease in Chronic Kidney Disease

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INTRODUCTION

Acute or chronic dysfunction in the heart or kidneys can cause dysfunction in the other organ, producing cardiorenal syndromes that were classified in 2008 by Ronco and colleagues[1] into five different types. In type I, or acute cardiorenal syndrome, an abrupt worsening of cardiac function leads to acute kidney injury. In type II, or chronic cardiorenal syndrome, chronic cardiac dysfunction causes progressive and potentially permanent chronic kidney function impairment. In type III, or acute renocardiac syndrome, an abrupt worsening of kidney function causes acute cardiac dysfunction. In type IV, or chronic renocardiac syndrome, chronic kidney dysfunction contributes to cardiac dysfunction. In type V, or secondary cardiorenal syndrome, a systemic condition such as diabetes mellitus or sepsis causes both cardiac and renal dysfunction. This chapter will focus on type IV, chronic renocardiac syndrome.

Both estimated glomerular filtration rate (eGFR) and albuminuria are independent predictors of cardiovascular (CV) events.[2] In over a million enrollers in the California Kaiser Permanente health maintenance organization (HMO), the degree of kidney function impairment independently and incrementally predicted subsequent cardiac events, hospitalization, and all-cause mortality.[3] Among 11,640 patients with type 2 diabetes, a tenfold increment in urinary albumin to creatinine ratio independently increased the risk of CV events by 2.5-fold and that of CV death by 3.9-fold.[4] Every halving of baseline eGFR was associated with a 2.2-fold increase in a risk of CV events and a 3.6-fold increase in risk of CV death.[4] In a recent meta-analysis, mortality risk was doubled at eGFR levels of 30 to 45 mL/min/1.73 m^2 or urine albumin to creatinine ratio > 11.3 mg per millimole as compared with their normal ranges.[5] Furthermore, patients with higher levels of proteinuria within a given level of eGFR had an increased risk of adverse outcomes.[6]

Not only is the baseline eGFR predictive of CV events, but so is the rate of decline of eGFR. The Cardiovascular Health Study demonstrated that those that had a more rapid decline in eGFR over a 7-year period had increased risk of CV events during the subsequent 8-year period: an increased risk of heart failure of about 30% and an increased risk of myocardial infarction (MI) of about 40%.[7] In the U.S. Atherosclerosis Risk in Communities (ARIC) study, individuals with greatest annual declines in eGFR had higher risk of incident coronary heart disease and of all-cause mortality at 3 and 9 years than those with stable eGFRs.[8]

In the Cardiovascular Health Study, the 3-year probability of CV events increased as the GFR declined below 70 mL per minute.[9] However, the probability decreased substantially after adjustment for traditional risk factors. Below a eGFR level of 30 mL per minute, the CV event rate is very high and likely influenced by uremia-related risk factors. After starting dialysis therapy, atheromatous event rates are much higher than before dialysis. In the United States, the incidence of de novo coronary events, stroke, and peripheral vascular disease of hemodialysis patients, after 2.2 years follow-up from the start of dialysis, were 10.2%, 2.2%, and 14%, respectively.[10] In addition, the uremic state is certainly cardiomyopathic and predisposes the patient to heart failure. This is supported by numerous studies: a high incidence of heart failure in CKD,[11] a high prevalence of cardiac failure on starting dialysis,[12] a higher rate of de novo symptomatic heart failure in renal transplant recipients than in the general population,[13] and a high incidence of de novo cardiac failure in hemodialysis patients (13.6% over a 2.2-year mean follow-up in the United States and 17% over a 3.4-year follow-up in Canada).[14,15]

The rate of CV death in patients on dialysis is substantially higher than that of the general population in all age groups, particularly in the younger group (Fig. 79.1).[16] This enormous burden of cardiac disease is related to the high prevalence of different cardiac/vascular diseases, the high rate of traditional cardiac risk factors, and the cardiopathic and vasculopathic hemodynamic and metabolic milieu associated with chronic kidney disease (CKD).

The Pathogenesis of Cardiac Disease

The CV disorders associated with CKD are multiple and often present in the same patient (Fig. 79.2). Atherosclerotic events occur frequently among patients with CKD[11]

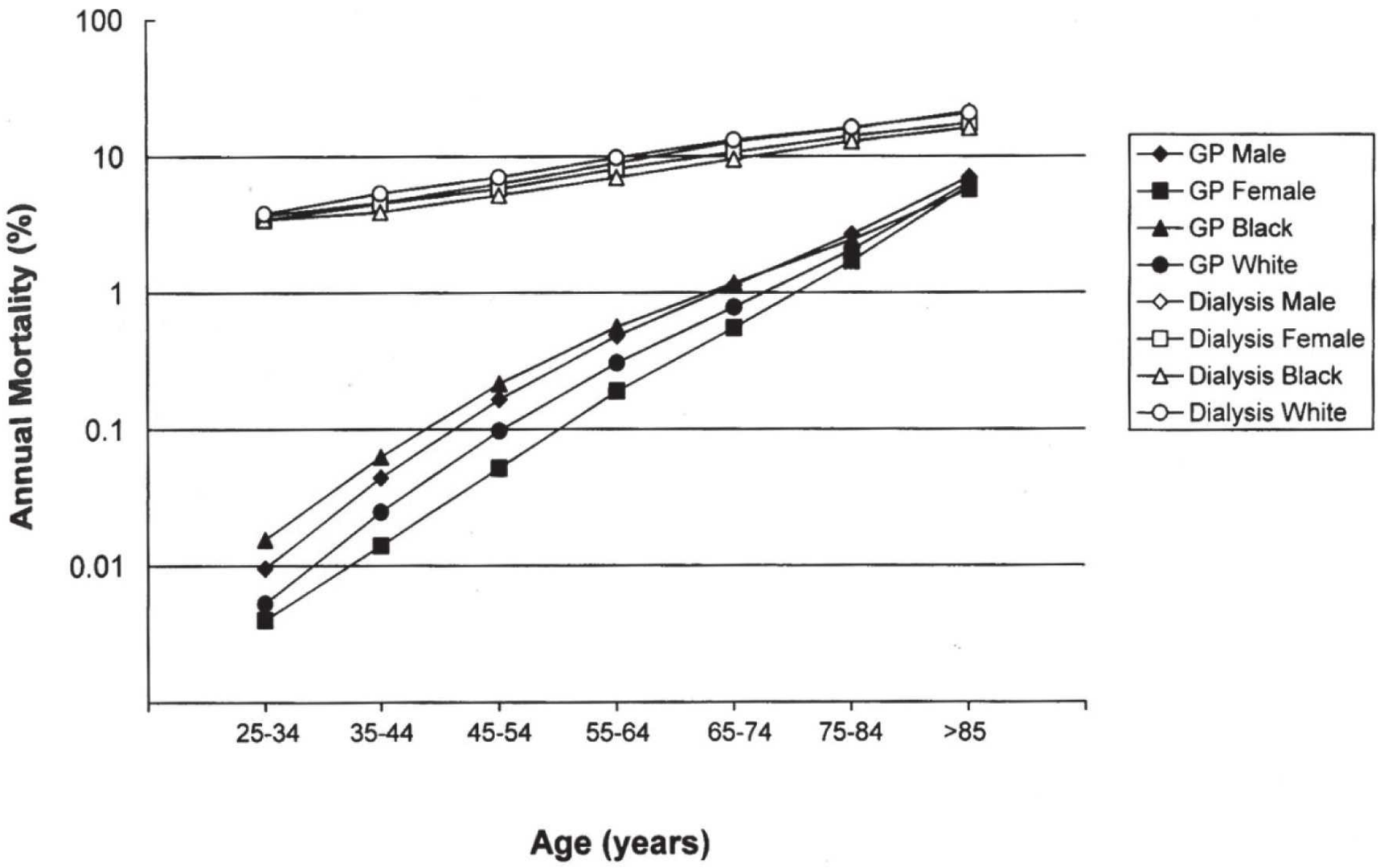

FIGURE 79.1 Annual cardiovascular mortality by age group in the general population (GP) and in patients on dialysis. (From Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol.* 1998;9:S16, with permission.)

because of the high prevalence of diabetes, hypertension, dyslipidemia, and the likelihood that uremia-related factors increase atherosclerotic risk, particularly when eGFR falls below 30mL/min/1.73 m^2. Arteriosclerosis, a diffuse disorder of large conduit arteries, is characterized by dilated, ectatic, noncompliant vessels. Such noncompliance can be exacerbated by metastatic vascular calcification.[17]

Concentric left ventricular hypertrophy (LVH) also occurs frequently because of LV pressure overload caused by hypertension, arteriosclerosis, and sometimes aortic stenosis.[18] Eccentric LVH results from LV volume overload associated with hypervolemia, arteriovenous fistula, and anemia. During years on dialysis LV growth occurs,[19] although it regresses following renal transplantation.[20] LVH can progress

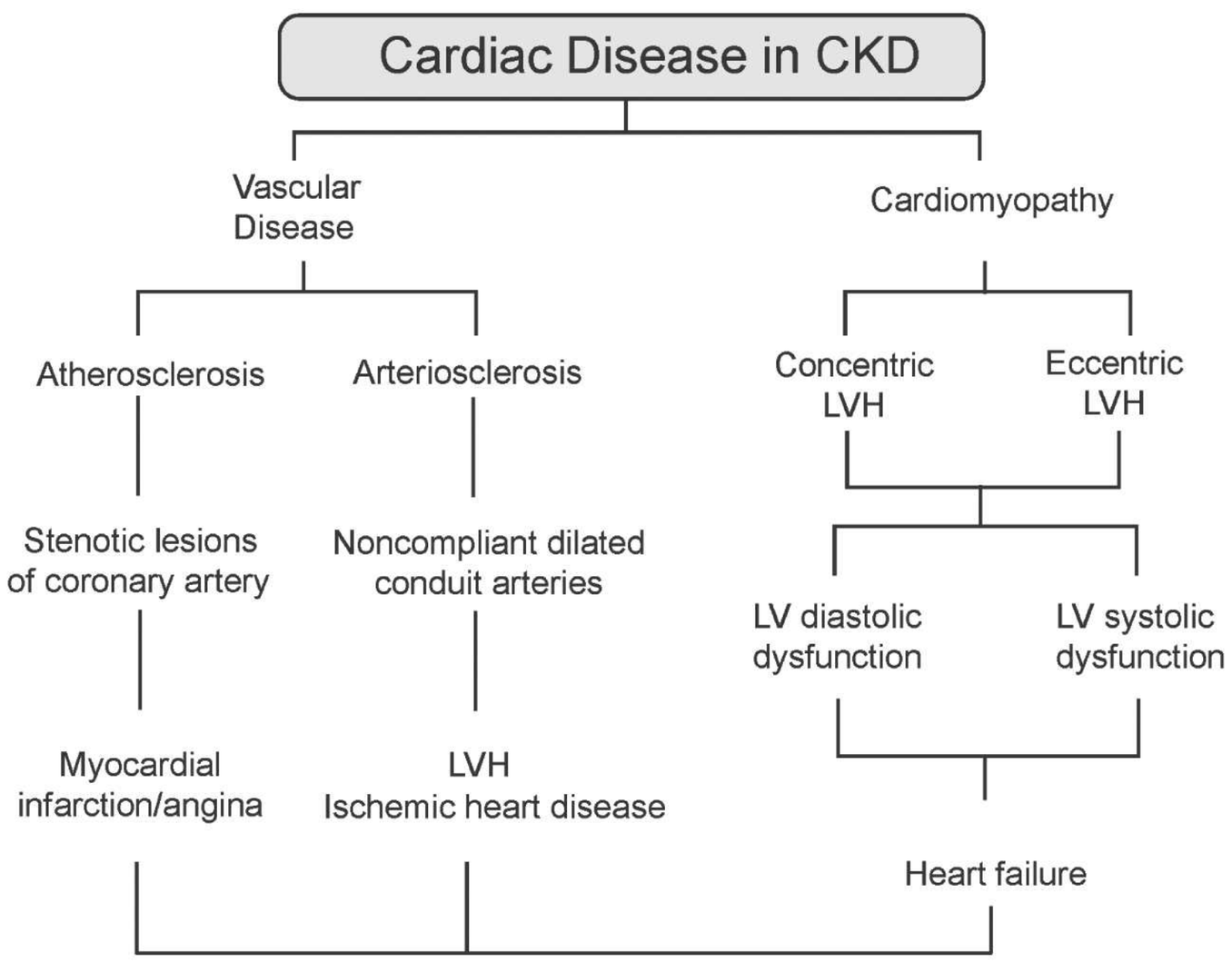

FIGURE 79.2 The pathogenesis of cardiovascular disease in chronic kidney disease (CKD). *LV,* left ventricular; *LVH,* left ventricular hypertrophy.

to LV systolic dysfunction through progressive myocyte loss, but LV diastolic dysfunction also frequently results in symptomatic pulmonary edema.[21]

Ischemic Heart Disease

Coronary artery disease. Symptomatic myocardial ischemia usually results from flow-limiting critical coronary atherosclerotic disease, but may be present in the absence of significant angiographic disease in approximately 25% of patients (Fig. 79.3).[22] In the latter case, small-vessel disease or a decrease in myocardial capillary density consequent to LVH or fibrosis may contribute to the ischemic symptoms.[23–25] LVH itself may predispose the patient to ischemia, and it may be associated with increased diastolic coronary blood flow caused by arteriosclerosis.

In non-CKD populations, the initiating event of atherosclerosis appears to be endothelial injury caused by mechanical stress (e.g., hypertension) or endothelial toxins (nicotine, oxidative stress, hyperlipidemia, and inflammation) that alter the endothelial phenotype to a more permeable, procoagulant state.[26] Endothelial denudation or, more commonly, alterations in cell surface receptor expression, permits the access of lipoproteins and macrophages into the subintimal space.[26,27] The oxidative modification of lipoproteins, particularly of low-density lipoprotein (LDL), is chemotactic for macrophages and facilitates the uptake of oxidized lipids by macrophages, resulting in the formation of foam cells.[28] Oxidized LDL stimulates the elaboration of growth factors that are mitogenic for smooth muscle and are profibrotic.[29] These processes result in the accumulation of oxidatively modified lipids and inflammatory cells at the center of a fibrous "cap" of variable thickness. This cap may rupture, causing subocclusive thromboses that may be minimally symptomatic or associated with acute coronary syndromes (e.g., unstable angina, myocardial infarction). These thrombi eventually become organized in the wall of the vessel. Calcific deposits may develop. The mature atheroma thus may contain, in addition to lipids, inflammatory cells, collagen, an organized thrombus, and calcium.[30] The propensity for rupture varies with the composition of the atheroma. Lipid and inflammatory cell–rich atheromas with thin fibrous caps are thought to be more

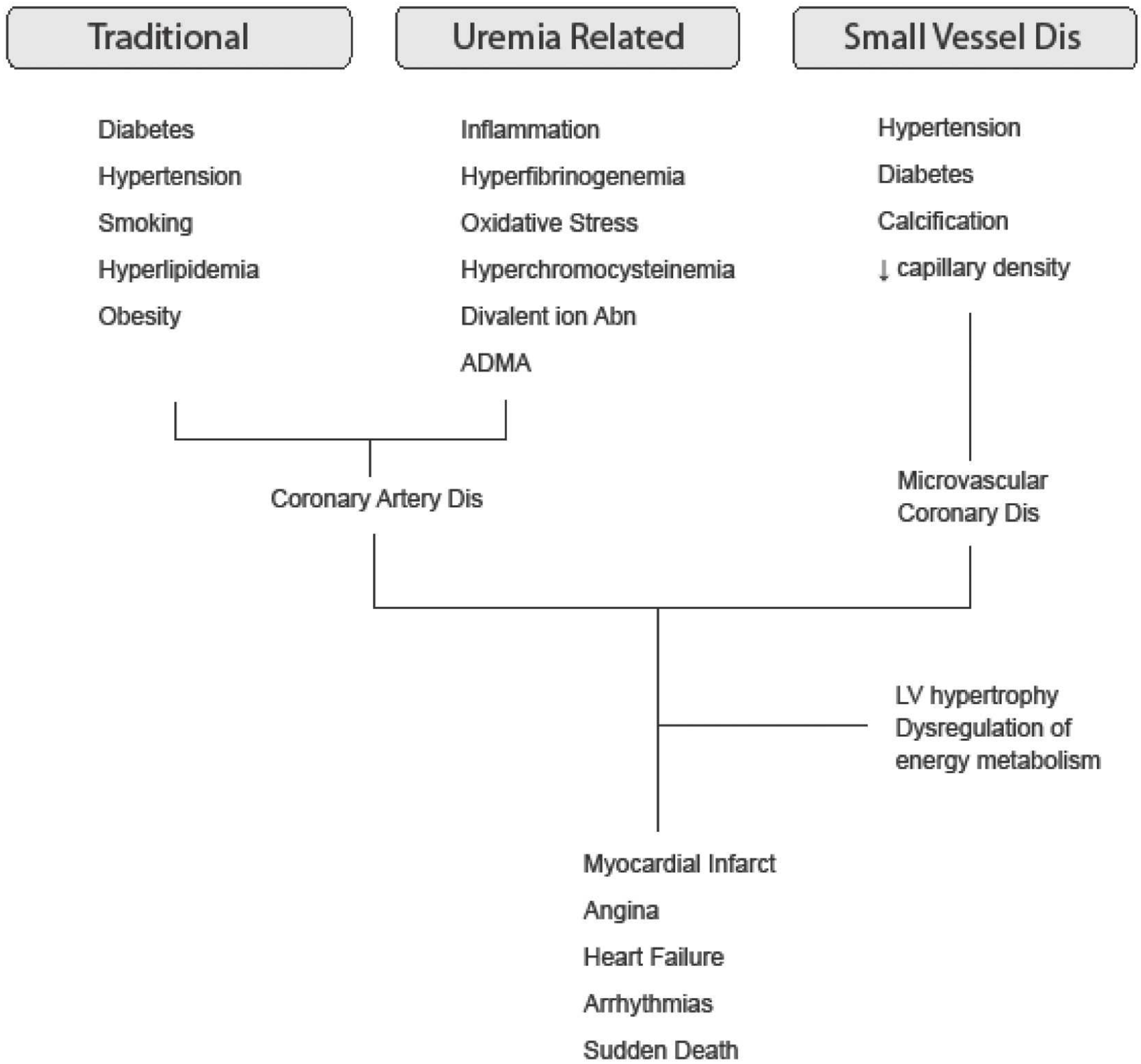

FIGURE 79.3 The etiology of ischemic heart disease in chronic kidney disease. *Dis,* disease; *ADMA,* asymmetric dimethyl arginine; *LV,* left ventricular

unstable than those with a greater degree of fibrosis and those that are less lipid.[31]

The histologic classification of coronary artery disease (CAD) lesions is outlined in Figure 79.4.[32] Initial lesions, type I through III, are small and silent, whereas types IV to VI may produce clinical events or may remain silent. The riskiest lesion is type VI, where surface defects and hematoma and a thrombus occur. The anatomic study of carotid plaque composition in 46 CKD patients with critical stenosis was compared to plaques in 56 CAD patients with normal renal function.[33] In CKD patients compared to controls, plaques were more frequently unstable (83% versus 52%), ruptured (59% versus 36%), and calcified (17% versus 7%), and the fibrous component was reduced (40% versus 57%).

Postmortem data from patients with CKD show increased vascular medial thickness and a smaller lumen area relative to control subjects matched for age and gender.[31] Although carotid artery intima-media thickness is a marker of atherosclerotic plaques in the general population, in CKD it may be increased by factors unrelated to atherosclerosis. In 406 patients with CKD and without overt CV disease (CVD), intima-media thickness was inversely correlated with eGFR, but had no association with traditional CV risk factors.[34] Furthermore, following a renal transplantation, intima-medial thickness normalized within 90 days. It is possible that shear stress associated with fluid overload, endothelial dysfunction, or other factors induce the increase in intima-media thickness seen in CKD.

Theoretically, renal failure can modify the atherogenic process at multiple levels. Hypertension and flow overload may increase stresses on the vascular wall at bifurcations. In many patients on dialysis, a prooxidant and chronic inflammatory state pertains, and both may contribute to endothelial dysfunction.[35] Hyperhomocysteinemia may promote endothelial activation and thrombosis by mechanisms that are yet unclear.[36] Hyperparathyroidism and divalent ion abnormalities may promote vascular calcification and medial hypertrophy.[17] The presence of calcium identified by electron beam tomography correlates with advanced atherosclerosis and appears to be more prevalent in patients with end-stage renal disease (ESRD).[37–38]

Asymmetric dimethyl arginine (ADMA) is an endogenous competitive inhibitor of nitric oxide synthase (NOS) and reduces nitric oxide generation, thus inhibiting the beneficial affect of nitric oxide on vasodilation, arterial stiffness, and endothelial function. The accumulation of ADMA inhibits NOS in endothelial cells and induces endothelial dysfunction, vasoconstriction, and atherosclerosis. ADMA levels are inversely related to GFR in patients with mild-to-moderate CKD. In renal transplant recipients, ADMA levels were an independent and a significant risk factor for major cardiac events and all-cause mortality.[39] A similar association was previously reported for dialysis patients.[40]

Matrix metalloproteinases and their specific tissue inhibitors regulate the proteolysis of the vascular extracellular matrix, and their balance is important in atherosclerosis and plaque destabilization. A cross-sectional study of 111 patients with stage 1 through 4 CKD, 217 dialysis patients, and 50 healthy controls demonstrated elevated levels of circulating metalloproteinase-10 associated with a severity of CKD.[41] A composite atherosclerosis score was highest in dialysis patients, and the severity of atherosclerosis was associated with the elevated levels of circulating metalloproteinase-10. It is possible that the riskier plaques seen in CKD may be caused, at least in part, by the high levels of metalloproteinases.

Microvascular disease. In the absence of flow-limiting CAD, ischemic symptoms may result from a reduction in coronary vasodilator reserve and altered myocardial oxygen delivery. Intracoronary ultrasonography has shown that angiographically normal vessel segments may contain areas of nonencroaching atheroma. Endothelial function is impaired in these vessels and may reduce coronary vasodilator reserve (i.e., the ability of the vessel to dilate above baseline in response to increased myocardial oxygen demand).[42] Vasodilator reserve is clearly impaired in vessels with lumen-encroaching disease.[43] The resulting mismatch of supply and demand may give rise to symptomatic ischemia.

Small vessel disease may occur in LVH and diabetes, and because of uremia per se. In LVH, small vessel smooth muscle hypertrophy and endothelial abnormalities can diminish coronary reserve. Diabetes may be associated with microvascular disease characterized by endothelial proliferation, subendothelial fibrosis, and exudative deposits of hyaline in the intima.[44] In uremic rats, LVH is associated with a severe reduction in myocardial capillary density compared with hypertensive rats that were matched for weight and blood pressure (BP).[25] Small vessel calcification may also impair coronary reserve.

Dysregulation of energy metabolism. An impairment in energy supply in the myocyte may increase cellular susceptibility to ischemia. A reduced myocardial phosphocreatine-adenosine triphosphate ratio under stress has been observed in uremic animals.[45] Hyperparathyroidism may play a critical role in the dysregulation of cellular energetics, and may thus exacerbate ischemic damage to the myocardium.[46]

Impaired myocardial fatty acid metabolism and insulin resistance, both of which reduce the synthesis of myocardial adenosine triphosphate, cause a deficiency in the myocardial energy supply. Visualization of impaired fatty acid metabolism is possible using single-photon emission computed tomography (SPECT) with the iodinated fatty acid analog iodine, 123-B-methyliodophenyl pentadecanoic acid (BMIPP). Uptake of this analog on SPECT images has been graded in 17 segments using a 5-point scale, and provides a measure of recurrent myocardial ischemia.[47] Among 155 prevalent hemodialysis patients without obstructive coronary artery disease on angiography, subsequent cardiac death was associated with both BMIPP score $>$ 12 and also with increased insulin resistance scores, suggesting an important role for impairment in

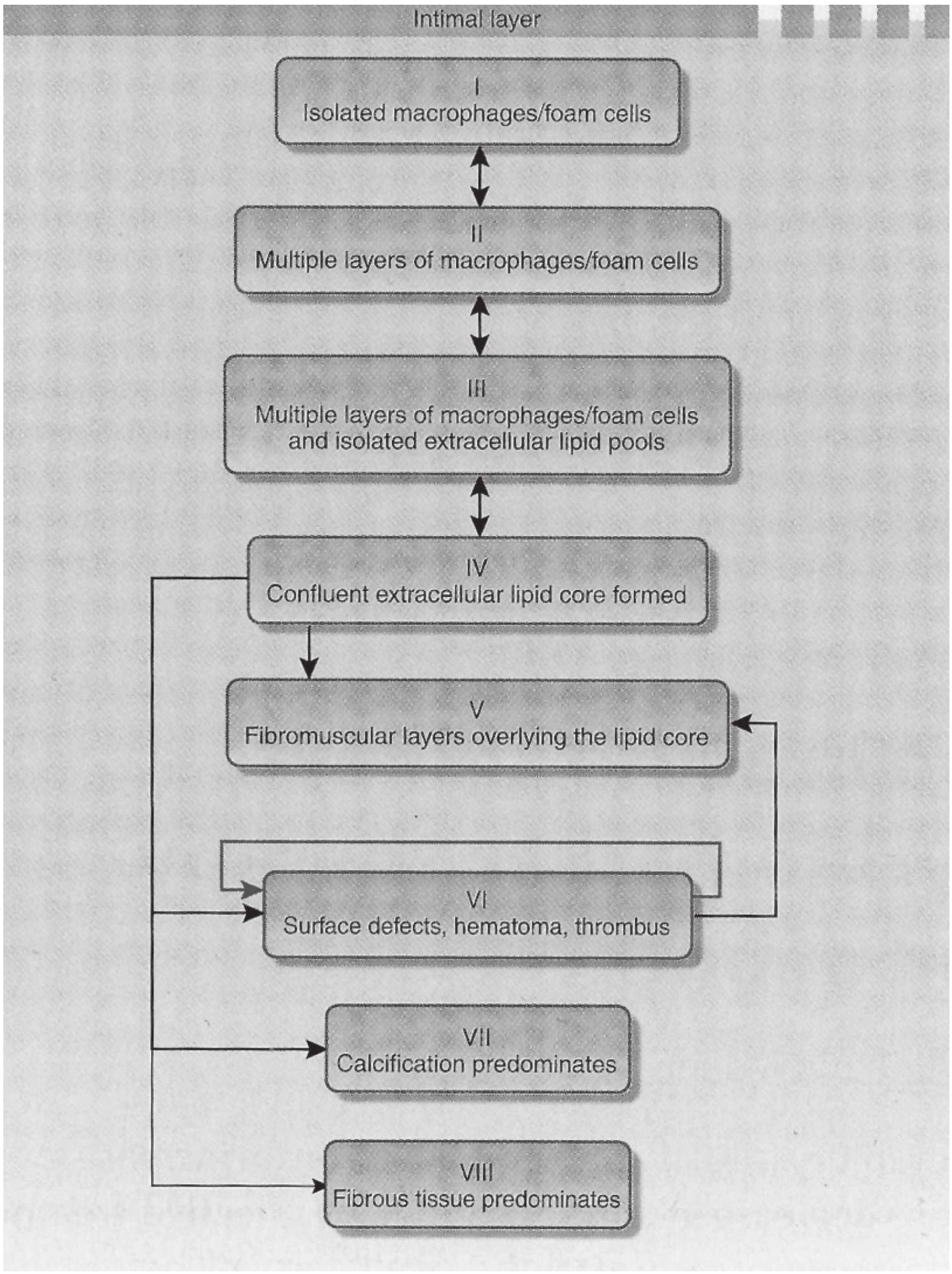

FIGURE 79.4 The histologic classification of atherosclerotic lesions. Thick lines identify preferential pathways of lesion evolution. Box VI highlights type VI plaques, which are the riskiest lesions. The line above it identifies a vicious cycle that may rapidly lead to vessel occlusion. (From Zoccali C, Secks S. What makes plaques vulnerable in CKD?: a fresh look at metalloproteinases. *Kidney Int*. 2010;78:1207, with permission.)

myocardial energy supply in the occurrence of cardiac death in these patients.[47] In a prospective study of a larger group (N = 318) of asymptomatic hemodialysis patients without a clinical history of MI or coronary revascularization who were followed for 3.6 ± 1 year, a BMIPP score > 12 was again strongly associated with cardiac death (hazard ratio [HR]: 22; 95% confidence interval [CI] = 8.5 to 56.1).[48]

Arteriosclerosis

Increased CV morbidity and mortality have been correlated, either directly or indirectly, with various estimates of elevated LV afterload in patients with CKD.[49–51] Postulated etiologic factors include increased arterial wall stiffness,[49] raised sympathetic tone mediated by elevated noradrenaline levels,[52,53] cardiac natriuretic peptides,[54] nocturnal hypoxemia,[55] and autonomic dysregulation.[56] These factors are associated with two established components of LV afterload: hypertension and reduced arterial wall compliance. Before examining these, however, it is important first to recognize the pathophysiologic similarities and differences by which they are characterized.

Hypertension has usually been attributed to a reduction in the caliber or number of muscular arteries (150 to 400 μm diameter), resulting in an increase in peripheral resistance. This approach, however, does not take into account the fact that BP fluctuates during the cardiac cycle, and that systolic and diastolic levels represent only the limits of this fluctuation. A Fourier analysis of the BP curve can determine both its steady state (mean BP) and oscillatory (fluctuation about the mean) components. The former is determined exclusively by cardiac output and peripheral resistance (pressure and flow considered constant over time). The oscillatory component is determined by the pattern of LV ejection, the viscoelastic properties of large conduit arteries, and the reflection of pulse waves.[57] A faster pulse wave velocity (PWV) is primarily associated with arterial stiffness, which, in CKD, is an acceleration of the normal aging process with vessel dilatation and a diffuse, nonocclusive medial and intimal wall hypertrophy (arteriosclerosis). It has been correlated with shortened stature, male gender, smoking, BP, diabetes, volume overload, humoral imbalance, and age.[58–60]

The clinical characteristics of hypertension therefore will depend on the predominant abnormality. Increased peripheral resistance is characterized principally by an increased diastolic and mean BP, whereas increased arterial stiffness and early wave reflections are indicated by an increased systolic and widened pulse pressure. Because the peripheral resistance of most dialysis patients is within the normal range, it is likely that effects from an accelerated PWV contribute more significantly to CV morbidity than an elevation in mean BP. Increased systolic BP and pulse pressure are observed in dialysis patients and are closely correlated with LV hypertrophy.[61,62]

Vascular calcification. An increased calcium X phosphate product, elevated levels of promoters of calcification, and reduced levels of inhibitors of calcification, in addition to hyperparathyroidism, insulin resistance, oxidant stresses, and dyslipidemia, promote metastatic vascular calcification and heart fibrosis in patients with ESRD.[63] Multiple inhibitors of vascular calcification have been identified, the transcription and synthesis of which are downregulated during inflammation. A study in a mouse model revealed that fetuin-A, an inhibitor of vascular calcification, protects against vascular calcification in CKD, suggesting that the patients who develop calcification might be those with inflammation and low levels of circulating inhibitors of vascular calcification.[64]

Vascular smooth muscle cells have the ability to transform into cells with chondrocytelike or osteoblastlike phenotypes, the consequences of which include the local production of collagen and noncollagenous proteins in intimal and medial layers, the incorporation of calcium and phosphorus into matrix vesicles, and vascular mineralization. This active process is associated with CKD, aging, diabetes, and inflammation.[63]

The cellular origin of medial vascular calcifications is suggested by ultrastructural analysis of the iliac arteries in 30 dialysis patients, obtained before renal transplantation, which demonstrated that arterial microcalcifications seem to originate from nanocrystals, and they often exhibit a core-shell structure.[65]

Two types of vascular calcification occur: patchy calcification of the intima associated with atherosclerotic plaques and diffuse calcification of the media, in the absence of cholesterol deposits, associated with arteriosclerosis. Metastatic vascular calcification decreases compliance of large conduit vessels and thus increases PWV. An early rebound of pressure waves from the distal vessels increases systolic pressure and predisposes the patient to LVH, and low diastolic pressure predisposes the patient to diminished coronary flow during diastole.

Controversy exists as to whether these are two distinct entities in CKD or rather are a continuum of advanced vascular pathology consistent with accelerated atherosclerotic calcification.[66,67] Coronary artery calcification scoring by computed tomography is used to estimate the likelihood of coronary artery disease in the general population and is a predictor of all-cause mortality. In 225 diabetic patients with proteinuria, coronary artery calcification was diagnosed in 86% of the patients, and it was not associated with eGFR, serum calcium, phosphate, parathyroid hormone, or 25-hydroxy vitamin D.[69] This suggests that the coronary calcification was associated with atherosclerotic disease rather than medial calcification induced by CKD. The severity of coronary artery calcification early in the course of CKD was an independent predictor of all-cause mortality.[68]

A recent autopsy study[69] of patients at different stages of CKD reported the occurrence of coronary intimal sclerosis in all CKD stages, but medial sclerosis in patients with stage 4 and 5 CKD (18%). Moreover, medial calcification was generally associated with intimal sclerosis, which is supportive

of the belief that medial calcification is an amplification of preexisting atherosclerosis.

Cardiomyopathy

Left ventricular hypertrophy. Ventricular growth occurs in response to mechanical stresses, primarily volume or pressure overload (Fig. 79.5). LV volume overload results in the addition of new sarcomeres in series, leading to an increased cavity diameter.[70] A larger diameter results in increased wall tension, a direct consequence of the Laplace law, which states that all wall tension (T) is proportional to the product of intraventricular pressure (P) multiplied by the ventricular diameter (D), divided by the wall thickness (M), or T = PD/M. An increase in wall tension secondarily stimulates the addition of new sarcomeres in parallel. This remodeling thickens the ventricular wall, distributing the tension over a larger cross-sectional area of muscle and returning the tension in each individual fiber back to normal, thereby alleviating the stimulus to further hypertrophy. This combination of cavity enlargement and wall thickening is called eccentric hypertrophy. Pressure overload increases wall tension by increasing the intraventricular pressure, resulting directly in the parallel addition of new sarcomeres and their functional consequences, as described. Because sarcomeres are not added in series, isolated pressure overload does not lead to cavity enlargement (concentric hypertrophy).

Both eccentric and concentric hypertrophies are initially beneficial. Dilation permits an increase in stroke volume without an increase in the inotropic state of the myocardium and, as such, is an efficient adaptation to volume overload.[70] It also permits the maintenance of normal stroke volume and cardiac output in the presence of decreased contractility. Muscular hypertrophy returns the tension per unit muscle fiber back to normal, thereby decreasing ventricular stress.

The uremic milieu of chronic renal disease can potentiate many of these processes. Anemia, salt and water excess, and arteriovenous fistulae in patients on dialysis are prevalent causes of volume overload, whereas hypertension is a major cause of pressure overload. These disturbances are probably the primary stimuli to ventricular remodeling in uremia. These same stimuli promote arterial remodeling in the large

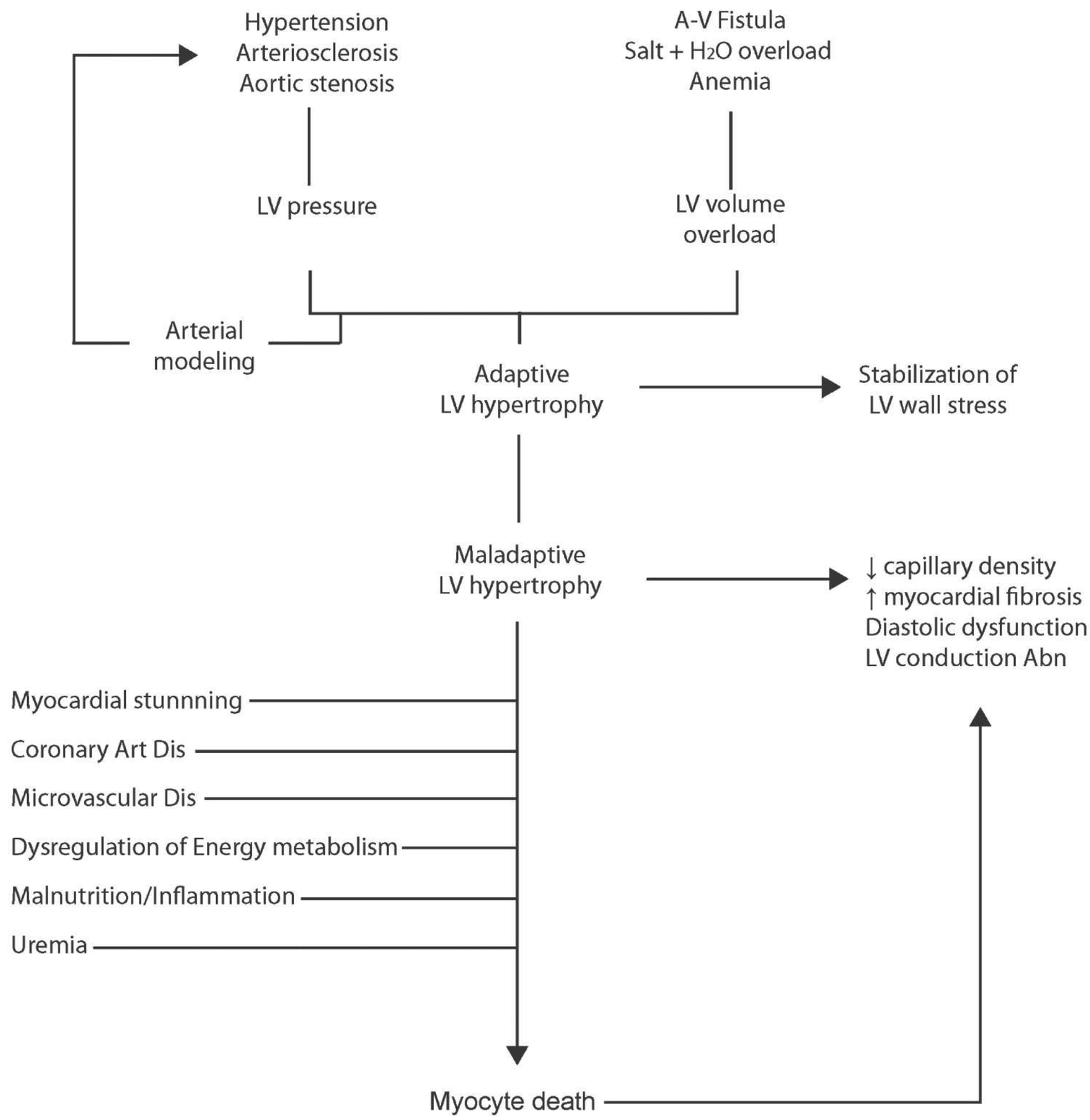

FIGURE 79.5 The evolution of cardiomyopathy in chronic kidney disease. *A-V,* atrioventricular; *LV,* left ventricular; *Art Dis,* artery disease; *Dis,* disease.

and resistance arteries, which is characterized by diffuse arterial thickening and stiffening (arteriosclerosis), which can increase the effective load on the left ventricle independently of mean arterial pressure.[71,72] Secondary hyperparathyroidism and raised calcium phosphate product may be associated with aortic valve calcification and, in some cases, stenosis, which is a less frequent cause of pressure overload.[73]

Progressive concentric LVH and hyperkinesis occur in hemodialysis patients, which is partly explained by hypertension but not by a wide array of potential risk factors, including moderate anemia.[19] Another explanation may be that primary stimuli independent of LV load might initiate or contribute to LVH and fibrosis in patients with CKD. Several signaling pathways could have a role in this process, including defects in insulin signaling through the protein kinase, Akt, and downstream, the mammalian target of rapamycin (mTOR) pathway.[74] Siedlecki et al.[75] created normotensive CKD using a mouse model in which kidney parenchyma was resected so as to avoid excessive renin-angiotensin system (RAS) activation. Progressive LVH and fibrosis developed, which was associated with de novo protein synthesis and activation of the mTOR pathway. The administration of rapamycin, which inhibits the mTOR pathway, prevented cardiac hypertrophy.

Myocyte death. Ultimately, in persistent LV overload, LVH becomes maladaptive (Fig. 79.5). Muscular hypertrophy is associated with several progressive, deleterious changes in cell function and tissue architecture. Early in the evolution of LV hypertrophy, slow reuptake of calcium by the sarcoplasmic reticulum leads to abnormal ventricular relaxation. Combined with decreased passive compliance of a thickened ventricular wall, these changes may precipitate diastolic dysfunction.[76] More advanced sarcoplasmic reticulum dysfunction is associated with calcium overload and cell death. Decreased capillary density, impaired coronary reserve, and abnormal relaxation may decrease subendocardial perfusion, promoting ischemia.[25,77] The frequent coexistence of CAD may exacerbate ischemia and myocyte attrition. Fibrosis of the cardiac interstitium also occurs and appears to be more marked in pressure than in volume overload.[77] Myocyte apoptosis, ischemia, and neurohormonal activation (e.g., increased catecholamines, angiotensin II, and aldosterone) are thought to contribute to myocardial dysfunction.[78,79] In the late phases of chronic and sustained overload, oxidative stress may contribute to cellular dysfunction and demise.[35] Together, these various processes lead to progressive cellular attrition, fibrosis, pump failure, and, ultimately, death.

The attrition of myocytes in chronic uremia may be exacerbated by several factors. An underlying coronary artery disease promotes ischemia and infarction. Hyperparathyroidism increases susceptibility to ischemia through dysregulation of the cellular energy metabolism,[46] and appears to promote myocardial fibrosis directly.[80] Malnutrition, oxidative stress, and inadequate dialysis may additionally promote myocyte death. Such cell death in the presence of LVH and continuing pressure and volume overload may be catastrophic, leading to a severe overload cardiomyopathy and, ultimately, death.[81]

Pathologic studies support this etiologic pathway. Cardiac pathology in patients who had diabetes, heart failure, and no evidence of coronary artery disease on angiography revealed cell loss as a result of apoptosis and necrosis of cardiac myocytes and endothelial cells, with the extent of fibrosis, apoptosis, and hypertrophy all greater in hypertensive patients than in those without hypertension.[82] Myocardial biopsies of dialysis patients with dilated cardiomyopathy revealed abnormal cardiac myocyte anatomy and interposition of dense fibrosis.[83] The extent of myocardial fibrosis in patients with ESRD was more marked than in patients with diabetes mellitus or essential hypertension with similar LV mass.[84]

Myocardial stunning. Another cardiopathic mechanism that may predispose to a patient arrhythmia or to heart failure is recurrent reperfusion injury. The coronary arteries of dialysis patients are often narrowed, the microcirculation is often underdeveloped, and the LV may be hypertrophied. In this scenario, transient hypoperfusion could produce severe ischemia, followed by reperfusion necrosis.[85] The frequent, although minor elevations in troponin observed in ESRD patients may reflect this myocardial damage. A phenomenon called myocardial stunning supports this hypothesis.

Myocardial stunning has been defined as a 20% reduction in regional wall motion in two or more segments and hyperkinesis as either a $>$ 20% or a $>$ 50% increase in shortening fraction. This was measured using echocardiography before hemodialysis, during hemodialysis, and 15 minutes after hemodialysis in 12 children without structural cardiac disease. Eleven of the 12 developed myocardial stunning with varying degrees of compensatory hyperkinesis in unaffected segments, thus maintaining LV ejection fraction throughout dialysis.[86] This regional hypokinesis is associated with reduced myocardial blood flow. Four patients without coronary artery disease had myocardial blood measured during dialysis using serial intradialytic $H_2{}^{15}O$ positron emission tomography scanning and had their regional wall motion assessed using serial concurrent echocardiography.[87] Segmental myocardial blood flow was reduced to a significantly greater extent in areas that developed regional wall motion abnormalities compared with those that did not.

Valvular Disease

Most valvular lesions observed in patients with CKD are acquired and develop from dystrophic calcification of the valvular annulus and leaflets, particularly the aortic and mitral valves.[88] The prevalence of aortic valve calcification in dialysis patients is up to 55%, similar to that in the elderly general population, although it occurs 10 to 20 years earlier.[88,89] Aortic valve orifice stenosis in CKD evolves from valve sclerosis, which itself is now generally recognized to be associated with an increased cardiovascular mortality.[90] In dialysis patients, the prevalence of aortic stenosis is 3% to 13%.[45] It

may sometimes evolve rapidly (within 6 months) to hemodynamically significant stenosis, with a worsening of LVH and rapidly evolving symptoms. Age, duration of dialysis, a raised phosphate level, and an elevated calcium phosphate product appear to be the most important risk factors for the development of aortic stenosis.[88]

Mitral valve calcification is not as common as aortic valve disease in CKD and may have a somewhat different pathophysiology. In one study[88] evaluated by echocardiography, mitral annulus calcification was present in 45% of 92 hemodialysis patients (compared to 10% of age-and gender-matched controls). In a study[91] of 135 peritoneal dialysis patients with low parathyroid hormone levels, a constant involvement of the posterior cusp, together with left atrial enlargement, was observed. Valve calcification has also been associated with rhythm and cardiac conduction defects, valvular insufficiency, and peripheral vascular calcification. Although most studies have identified abnormalities in calcium phosphate metabolism as the predominant underlying risk factor, additional factors include the duration of dialysis and the duration of predialysis systolic hypertension. Factors associated with decreased survival include the severity of calcification, mitral regurgitation, and reduced LV function.[92]

Diagnosis

Coronary Artery Disease

Symptoms of myocardial ischemia in patients with CKD are, in general, similar to those in the nonuremic population. However, the prevalence of silent myocardial ischemia in this group of patients is very high.[93,94] This has been best demonstrated in diabetic patients with ESRD because they often are subjected to a screening coronary angiography before renal transplantation. In one series[95] of 100 diabetic patients with ESRD, for example, 75% of the patients with angiographically demonstrated CAD had no typical angina symptoms. The prevalence of asymptomatic CAD in nondiabetic patients with ESRD is not as well studied. Exertional dyspnea is also less specific for cardiac disease in patients with CKD than in the general population. Such symptoms may be attributable to anemia, acidosis, heart failure, or fluid overload; therefore, a careful interpretation within the clinical context is required.

Patients with CKD and symptomatic ischemic heart disease (IHD) should be investigated in a manner similar to patients with normal renal function, provided that revascularization will be considered should critical coronary artery disease (CAD) be identified. Routine screening for CAD in asymptomatic patients with CKD therefore is not recommended.[96] It is appropriate to apply clinical practice guidelines for a CAD screening of patients before noncardiac surgery to the CKD population as well.[97] Generally, CAD screening is recommended before surgery when the combination of risk factors and the nature of the operation place the patient at moderate or higher risk of a cardiovascular event. Patients being evaluated for renal transplantation are an exception to the aforementioned recommendations. The adverse prognostic implications of CAD, the desire to avoid allograft injury from posttransplantation invasive cardiac testing, and the need to ration transplantable organs are justification for screening all but the lower risk patients. The American Society of Transplant Physicians has published guidelines for the evaluation of renal transplantation candidates that include recommendations for the investigation of CAD.[98]

Biomarkers for ischemic heart disease. Cardiac troponin T and troponin I are currently the standard biomarkers of myocardial injury. These tests are more specific for myocardial damage than creatinine kinase-myocardial band but still are not always indicative of an ischemic mechanism of injury.[99] First-generation troponin T levels in ESRD patients are often high, whereas troponin I levels are high less frequently.[100] Although there is no difference between the diagnostic and prognostic accuracy of troponin T versus troponin I in the general population in suspected acute coronary syndrome,[101] the lower incidence of increased troponin I in the renal failure population suggests that this is the preferred test in this clinical setting.[100]

Despite concerns about falsely positive tests, troponins are clearly very useful in the evaluation of suspected ACS. In one retrospective analysis,[102] troponin I was shown to be the best performing marker in suspected acute coronary syndrome (ACS) in patients with CKD or ESRD when compared to alternatives such as creatine kinase or myoglobin. Although troponin T is more likely to be elevated at baseline in patients with renal impairment, a normal level has useful negative predictive value. A sequential rise in either of the serum troponins is consistent with new myocardial damage regardless of symptoms.[103]

Noninvasive testing for coronary artery disease. Exercise electrocardiography (ECG) has been the traditional method of a noninvasive diagnosis of CAD. The sensitivity of this test is only 50% to 60% for single vessel disease but is greater than 85% for triple vessel CAD in the general population.[104] These figures are based on the assumption that the patient reaches an adequate exercise level (i.e., 85% of the age-adjusted predicted maximal heart rate). A large proportion of patients with ESRD are unable to achieve this target because of poor exercise tolerance, anemia, poorly controlled hypertension, or the use of cardiac medications. One study[105] of 85 diabetic uremic patients showed that only 6 achieved an adequate exercise level. Pharmacologic agents, therefore, often are used for noninvasive testing for CAD in these patients. The diagnostic utility of dipyridamole-thallium testing in patients with ESRD is poor,[106] whereas that of dobutamine stress echocardiography is better,[107] and therefore may be the method of choice where it is available.

Nuclear scintigraphic scanning. Nuclear scintigraphy can be used both for the assessment of myocardial systolic function and for ischemia. The former method examines the

ejection fraction of the left and/or right ventricles and relies upon gated analysis techniques. Care must be taken with regard to associated valve regurgitation, which when present, can substantially confound functional estimates. If valve function is intact, accurate estimates of systolic function at rest and with exercise can be achieved.

The predominant role for nuclear scanning techniques, however, is in the assessment of myocardial ischemia, both as a screening tool in the work-up for transplantation and in cases of diagnostic uncertainty. Exercise-based studies as well as the use of dipyridamole to enhance vasodilation are commonly used, together with one or other of technetium-99m (^{99m}Tc)-labeled thallium, methoxyisobutylisonitrile (MIBI), or metaiodobenzylguanidine (MIBG). Inherent problems with scintigraphy must be taken into consideration. BP may be too high or too low to permit the safe administration of a vasodilatory agent; high endogenous circulating levels of adenosine may blunt the efficacy of dipyridamole; coronary flow reserve may be reduced due to LV hypertrophy and small vessel disease; and symmetrical coronary disease and/or a blunted tachycardic response due to autonomic neuropathy can mask significant pathology.[108,109]

Dahan and colleagues[110] found a positive and negative predictive value of 47% and 91%, respectively, for dipyridamole-thallium combined imaging in the diagnosis of coronary disease by coronary angiography in a study of 60 asymptomatic hemodialysis patients. It is likely that both on-site expertise and the recognized testing limitations in patients with CKD influence the utility of nuclear scanning and therefore dictate the interpretation and screening strategy for a particular center.

Computed tomography. Electron-beam ultrafast computed tomography–derived coronary artery calcification assessment relies upon the principle that coronary artery calcification is a reliable surrogate for significant coronary atherosclerosis, but this is far from certain in patients with CKD.[66,67] It has been used recently to demonstrate a reduction in coronary artery calcification after treatment with the non–calcium-containing medication sevelamer and with cinacalcet.[111,112] The role of this technique in evaluating risk or disease in transplant patients is unknown. Severe coronary artery calcification measured by electron beam–computed tomography in stage 3 through 5 CKD occurs much more frequently in diabetics (56%) than in nondiabetics (4%). In CKD stages 1 and 2, the prevalence was 10% in diabetics and 1% in nondiabetics.[113]

In the Multi-Ethnic Study of Atherosclerosis, 562 adults with eGFR $<$ 60 mL per minute had assessments of coronary artery calcification.[114] The prevalence of coronary artery calcification at baseline was 66%, and the incidence was 6.1% per year in women and 14.8% in men. Progression occurred in 17% of subjects per year across all subgroups, and diabetes was associated with a 65% adjusted risk of progression.

The accuracy and clinical utility of noninvasive testing for coronary artery disease was evaluated in 517 Dutch patients referred for an evaluation of chest pain symptoms, using coronary arteriography as the gold standard.[115] Stress testing was sufficient as a diagnostic test for patients with a low pretest probability of coronary disease based on their Duke classification clinical score. Computed tomography coronary angiography was useful in patients with intermediate pretest probability, because it could distinguish which patients required invasive angiography. In patients with high pretest probability, proceeding directly to invasive angiography, without a noninvasive test evaluation, was recommended.

Coronary angiography. Cardiac catheterization and coronary angiography remain the gold standard for the diagnosis of CAD. A major disadvantage associated with this mode of investigation is the potential for renal toxicity from radiocontrast agents. CKD, especially in diabetic patients, is a major risk factor for contrast-induced acute renal failure.[116] The risk of clinical nephrotoxicity is related to the severity of prior renal impairment. Although most patients who develop nephropathy eventually recover renal function, there is a risk that contrast administration may precipitate ESRD in patients with severe impairment in renal function at baseline. The risk of contrast nephropathy in high-risk patients may be reduced by using nonionic contrast media and a saline infusion. Many interventions to reduce the risk of nephropathy have been studied, but none have been shown to be consistently effective.[116] A number of trials using N-acetylcysteine in CKD patients have demonstrated a reduction in the incidence of contrast nephropathy, whereas others have not. A meta-analysis of this topic indicated that the relative risk of nephropathy is reduced by N-acetylcysteine (relative risk 0.65; 95% CI, 0.43 to 1.00), but there has been significant heterogeneity in studies to date.[117] Given its low cost and lack of adverse effects, it is reasonable to use N-acetylcysteine in high-risk patients prior to angiography. A large trial with clinically meaningful outcomes is still required before it can be universally recommended.

Arteriosclerosis

Aortic PWV is the best available measure of aortic stiffness and correlates well with a subsequent risk for CVD.[118]

Cardiomyopathy

Because echocardiography is widely available, simple, and reproducible, it has become the method of choice for the assessment of LVH. Systolic dysfunction is defined as an ejection fraction of less than 40%, which indicates impaired myocardial contractility. It often is associated with LV dilation (LV end-diastolic diameter $\geq$ 5.6 cm), which is defined echocardiographically as an LV cavity volume index greater than 90 mL per square meter.[119] Concentric LVH is characterized by a thickened LV wall ($\geq$ 1.2 cm during diastole) with normal cavity volume. LV mass index is a calculated parameter that reflects the degree of muscular hypertrophy in the LV. Epidemiologic studies in nonrenal patients have

established that the upper limits of LV mass index are 130 g per square meter for adult men and 102 g per square meter for adult women.[120] Values above these limits indicate hypertrophy. The calculation of LV mass and volume are not independent of volume status. As a result, patients should be euvolemic when the echocardiogram is performed. In patients on hemodialysis, it is important to standardize the time and conditions of the study in relation to the dialysis session and to have patients at their dry weight.

Cardiac magnetic resonance is a volume-independent technique to assess cardiac structure and LV mass. This technique is now used as a surrogate outcome measure in randomized controlled trials (RCTs).[121] Of 246 Scottish hemodialysis patients, 64% had LV hypertrophy using this technique, and the principal associations of LV mass were end-diastolic volume, predialysis BP, and calcium X phosphate product.[122]

In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial,[123] in patients with stage 3 and 4 CKD, the prevalence of LV hypertrophy using echocardiography at baseline was 47%, with eccentric hypertrophy more prevalent than concentric. During the study, LVH prevalence and mean LV mass index did not increase significantly, but LV geometry fluctuated considerably within 2 years in both groups.

Levin et al.[124] have reported a prevalence of LVH in 27% of patients with a creatinine clearance rate greater than 50 mL per minute, in 31% of those with clearances of 25 to 49 L per minute, and in 45% of those with clearances less than 25 mL per minute. In the prospective arm of this study, an association between rising LV mass index and falling GFR was observed. The overall prevalence of LVH among patients beginning dialysis was 75%.[125] In a large prospective cohort study, only 16% had normal echocardiograms at inception. Fifteen percent (15%) had systolic dysfunction, 28% had dilation with preserved contractility, and 41% had concentric LVH.[126] In a subset of these patients on dialysis who underwent yearly consecutive echocardiograms, LV mass index and LV cavity volume progressively increased, and the biggest increase occurred between baseline and 1 year.[127] This progressive LV growth was confirmed in a recent prospective study.[19]

In patients about to undergo transplantation, the distribution of echocardiographic abnormalities is similar to those in patients on dialysis: normal, 17%; concentric LVH, 41%; dilation, 32%; and systolic dysfunction, 12%.[128] In this longitudinal study, the proportion of patients with normal studies doubled (36%) and systolic function normalized in all patients with fractional shortening of less than 25% at 1 year posttransplantation.[128]

Clinical Manifestations

Myocardial Infarction or Angina

The most frequent manifestations of ischemic heart disease are MI and angina. The incidence rate of atherosclerotic events (MI, CV events, peripheral vascular disease) in predialysis CKD is very high. In a Medicare population of nondiabetic CKD patients, it was 36 per 100 patient years, and in diabetic CKD, it was 49 per 100 patient years.[11]

In Canada, a prospective study[12] demonstrated that by the time patients reach ESRD, the prevalence of angina was 21% and of patients who had had a MI, it was 18%. The annual incidence of angina or MI among Canadian patients on hemodialysis is 10%.[129] Among renal transplant recipients, the annual incidence of MI, revascularization, or death from MI was 1.5%.[130] In another study, the rate of de novo angina or MI was 1.22 per 100 patient years.[13]

Both traditional and nontraditional risk factors predict coronary heart disease in CKD. Results from the atherosclerosis risk in communities (ARIC) study[131] identified that independent of age, gender, and diabetes the following are risk factors: smoking, hypertension, hyperglycemia, and hypercholesterolemia. In addition to these traditional risk factors, nontraditional risk factors identified were increased waist circumference, hyperlipoproteinemia B, anemia, hypoalbuminemia, and hyperfibrinogenemia (Table 79.1).[131]

79.1 Traditional and Nontraditional Risk Factors as Predictors of Coronary Artery Disease in Chronic Kidney Disease (Results from the ARIC study)[131]

Traditional	Adjusted RR	95% CI
Age, 5 years	1.33	1.1–1.6
Male	3.96	2.25–6.2
Smoking	1.91	1.2–3.2
Hypertension	1.79	1.1–2.9
Systolic BP, 20 mm Hg	1.26	1.05–1.5
Glucose, 40 mg/dL	1.26	1.15–1.4
Diabetes	2.88	1.9–4.5
Total chol, 43 mg/dL	1.46	1.3–1.7
Nontraditional		
Waist circum, 13 cm	1.24	1.0–1.6
Apolipoprotein B, 29 mg/dL	1.28	1.1–1.5
Anemia	2.01	1.2–3.4
S. Albumin, 0.33 mg/dL	0.76	0.6–0.9
Fibrinogen, 69 mg/dL	1.23	1.1–1.4

ARIC, atherosclerosis risk in communities; RR, relative risk; CI, confidence interval; BP, blood pressure; chol, cholesterol; circum, circumference.

In an incident cohort of dialysis patients, independent predictors of de novo ischemic heart disease events were diabetes, hypertension, and hypoalbuminemia.[132] In an incident cohort of renal transplant recipients,[13] the major predictors were diabetes and hypertension, and in a more recent cohort study,[133] hypercholesterolemia was identified as a predictor of cardiac events.

Congestive Heart Failure

Congestive heart failure (CHF) may result from systolic dysfunction or diastolic dysfunction,[21] the latter occurring because of concentric or eccentric hypertrophy (Fig. 79.2). IHD is an additional independent predictor. Among patients with diastolic dysfunction, CHF results from impaired ventricular relaxation; this leads to an exaggerated increase in LV end-diastolic pressure for a given increase in end-diastolic volume. As a result, a small excess of salt and water can rapidly lead to a large increase in LV end-diastolic pressure, culminating in pulmonary edema. The development of CHF, even in the presence of salt and water overload, suggests an underlying cardiac abnormality. Because the management of diastolic dysfunction differs from that of systolic dysfunction, an echocardiogram of the left ventricle is useful in planning management.

Approximately half of patients with CHF have CKD, as defined by a GFR ≤ 60 mL per minute.[134] Differentiating type II chronic cardiorenal syndrome from type IV chronic cardiorenal syndrome may be difficult, because chronic heart failure may cause CKD, and CKD predisposes a patient to heart failure. In predialysis, CKD heart failure events occur as frequently as atherosclerotic events, particularly in patients with diabetic nephropathy; in nondiabetic CKD patients, the event rate was 31 per 100 patient years and in diabetic CKD patients it was 52 per 100 patient years.[11]

On starting dialysis, 35% of patients have had a previous episode of CHF.[12] A baseline history of CHF carries a twofold risk of death independent of age, diabetes, and heart disease.[125] The risk for the development of pulmonary edema requiring hospitalization or ultrafiltration after starting maintenance hemodialysis is 10% annually.[129] Among patients free of CHF at the initiation of dialysis, de novo CHF developed in 25% over 41 months of observation.[15] In a cohort of 244 CKD patients, 20% developed new or worsening cardiac symptoms, including a change in their CHF symptoms.[134] Renal transplant recipients who were free of cardiac disease 1 year after transplantation developed de novo CHF as frequently as de novo IHD (1.26 versus 1.22 events per 100 patient years, respectively).[13]

In an incident cohort of dialysis patients without a previous history of CHF, the significant predictors of the de novo development of CHF, independent of age, diabetes, and systolic dysfunction at baseline, were hypertension, anemia, hypoalbuminemia, and hypocalcemia.[15] It appears that factors that predispose a patient to volume or flow overload (e.g., anemia), pressure overload (e.g., hypertension), and cell death (e.g., malnutrition, hypocalcemia/hyperparathyroidism, and IHD) are associated with CHF in dialysis.

The presence of concentric LV hypertrophy, LV dilation, or systolic dysfunction at the time of ESRD therapy has been associated with progressively higher risks of congestive heart failure independent of age, sex, diabetes, and ischemic heart disease.[126] Furthermore, changes in echocardiographic measurements following the initiation of dialysis also predicted the development of heart failure.[135]

In a large cohort of renal transplant recipients (RTRs) without cardiac disease 1 year after transplantation, age, diabetes, gender, high BP, and anemia were identified as independent risk factors for de novo CHF.[13]

Arrhythmias

In patients without renal failure, LVH and CAD appear to be associated with an increased risk of arrhythmias. As outlined earlier, these cardiac diseases occur frequently in patients with CKD. In addition, serum electrolyte levels that can affect cardiac conduction, including potassium, calcium, magnesium, and hydrogen, are often abnormal or undergo rapid fluctuations during hemodialysis.

In cross-sectional studies, the prevalence of arrhythmias is high: between 68% and 88% for atrial arrhythmias, 56% to 76% for ventricular arrhythmias, and premature ventricular complexes were found in 14% to 21%.[136,137] Older age, preexisting heart disease, LVH, and digoxin therapy were associated with a higher prevalence and a greater severity of cardiac arrhythmias. However, because of the considerable variation in the frequency and severity of arrhythmias during and after dialysis, the clinical significance in a given patient is unclear.

Most atrial arrhythmias are of low clinical significance. However, a sustained, rate-related (fast or slow) impairment of LV filling can certainly produce hemodynamic consequences. The majority of the premature ventricular contractions are unifocal and number less than 30 per hour. The finding of high-grade ventricular arrhythmias in the presence of CAD has been associated with an increased risk of cardiac mortality and sudden death.[138] Dialysis-associated hypotension may precipitate high-grade ventricular arrhythmias.

Arrhythmias in peritoneal dialysis patients appear different from those in hemodialysis patients. Severe cardiac arrhythmias occurred in only 4% of 27 peritoneal dialysis patients compared to 33% of 27 hemodialysis patients.[139] Patients in both groups were matched for age, sex, duration of treatment, and etiology of chronic renal failure. The lower frequency of LVH, the maintenance of a relatively stable BP, the absence of sudden hypotensive events, and the significantly lower incidence of hyperkalemia in patients on peritoneal dialysis may explain the lower incidence of severe arrhythmias.

Atrial Fibrillation

The prevalence of atrial fibrillation in ESRD is extremely high, and it is associated with increased mortality in hemodialysis patients.[140] Of 17,513 randomly sampled patients in the

Dialysis Outcomes and Practice Patterns Study (DOPPS),[141] 2,188 (12.5%) had preexisting atrial fibrillation and the incidence of de novo atrial fibrillation during follow-up was 1 per 100 patient years. Advanced age, non-black race, higher facility mean dialysate calcium, prosthetic heart valves, and valvular heart disease were associated with a higher risk of de novo atrial fibrillation. The risk of ischemic stroke in the general population is best estimated with the CHADS2 score (1 point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes; 2 points for prior stroke or transient ischemic attack). The CHADS2 score identified approximately equal-sized groups of hemodialysis patients at low (< 2) and high risk (> 4) for subsequent strokes.

The prevalence of atrial fibrillation in predialysis CKD is also high and likely related to comorbidity rather than severity of CKD. Of 2010 nondialysis patients with CKD in two community hospitals in Chicago, 21% had atrial fibrillations.[142] This was associated with older age, white race, increasing left atrial diameter, lower systolic BP, and congestive heart failure, but was not associated with eGFR.

Registry data in the United States revealed that the cumulative incidence of new onset atrial fibrillation was 3.6% at 12 months and 7.3% at 36 months after renal transplantation, and declined below the demographics adjusted cumulative incidence on the waiting list by about 17 months.[143] Baseline independent predictors of atrial fibrillation included older recipient age, male gender, white race, renal failure from hypertension, and coronary artery disease. Transplant factors included donor age, delayed graft function, post-transplantation hypertension, anemia, new onset diabetes, MI, and graft failure.

Sudden Death

The proportion of deaths designed as sudden is similar in both patients with CKD and the general population. In a British community-based study,[144] approximately 70% of deaths were the result of cardiac disease, and roughly half of those cardiovascular deaths were sudden. Among diabetic hemodialysis patients in the Die Deutsche Diabetes Dialysis (4D) study in 178 German dialysis centers,[145] 26% of adjudicated cardiac deaths were sudden, whereas coronary artery disease, heart failure, and other cardiac etiologies were the cause of 9%, 6%, and 3% of the adjudicated deaths, respectively. A study of 4,120 deaths in the United States during a 2-year follow-up of 12,833 prevalent hemodialysis patients showed that the greatest percentage of all deaths (27%) was caused by sudden cardiac arrest, whereas other cardiovascular conditions (including CAD, vascular heart disease, cardiomyopathy, arrhythmia, pericarditis/cardiac tamponade, and pulmonary edema) accounted for 20% of all deaths.[146]

A high rate of sudden cardiac death in 5,830 dialysis patients who underwent coronary artery bypass (CABG) surgery in the United States was reported by Herzog et al.[147] All-cause and arrhythmias-related mortality were 290 and 76 deaths per 1,000 patient years, respectively. Deaths from sudden cardiac arrest or arrhythmia accounted for approximately 25% of all-cause deaths.

The rate of sudden cardiac death was also examined in 19,440 U.S. patients with CKD who had undergone cardiac catheterization at a single institution[148]: 522 sudden cardiac deaths occurred and 25% of cases had an eGFR < 60 mL/min/1.73 m^2. The sudden cardiac death rate increased with increasing severity of CKD; the hazard ratio (HR) for each 10 mL/min/1.73 m^2 decline in eGFR was 1.11 (95% CI = 1.06 to 1.7).

Among patients undergoing dialysis, the frequency of sudden cardiac death increased both with the duration of time that the patient had been undergoing dialysis and with the duration of time since their previous dialysis session, and was highest among individuals with diabetes.[149,150] Furthermore, the ratio of observed to expected deaths was higher than expected in the first 12 hours after the initiation of the hemodialysis session, and increased as the time from start of the dialysis session exceeded 36 hours.[150] The number of observed deaths was three times higher than expected in the period 60 to 72 hours after the start of the dialysis session. Other risk factors for sudden death included hospitalization within the past 30 days and a decrease in systolic BP of 30 mm Hg during hemodialysis.[150] Patients with ESRD and diabetes have a higher risk of sudden death than nondiabetic ESRD patients, with an incidence of 20% within the first 2 years after the dialysis is initiated.[151]

Cardiac arrest. Four hundred cardiac arrests occurred in a total of 5,744,708 hemodialysis sessions, which is equivalent to a rate of 7 arrests per 100,000 hemodialysis sessions.[149] In another cohort study of 295,913 incident dialysis patients surviving at least 1 year on dialysis, the rate of cardiac arrest was 93 events per 1,000 patient years at year 1, and 164 events per 1,000 patient years at year 4.[152] Among patients with diabetes who were undergoing dialysis, the rate of cardiac arrest at year 1 was 110 events per 1,000 patient years, rising to 208 events per 1,000 patient years at year 4.[152]

The survival rates following cardiac arrest reported by Herzog[152] were 32% at 30 days and 17% at 1 year after arrest, respectively, and dropped to 13% at year 1 in patients with diabetes. On the other hand, 60% of patients with ESRD who experienced cardiac arrest in the dialysis unit died within 48 hours of cardiac arrest; 13% of these deaths occurred while in dialysis units.[149]

Mechanisms of sudden death. Clearly, the adverse cardiomyopathic and vasculopathic milieu predisposes individuals with CKD to arrhythmias and conduction abnormalities, which are manifestations of cardiac disease associated with sudden cardiac death. This predisposition is likely exacerbated by electrolyte shifts, increased ultrafiltration volumes, divalent ion abnormalities, diabetes, and sympathetic overactivity, in addition to inflammation and possibly iron deposition (Fig. 79.6). Impaired baroreflex effectiveness and sensitivity, as well as obstructive sleep apnea, might also

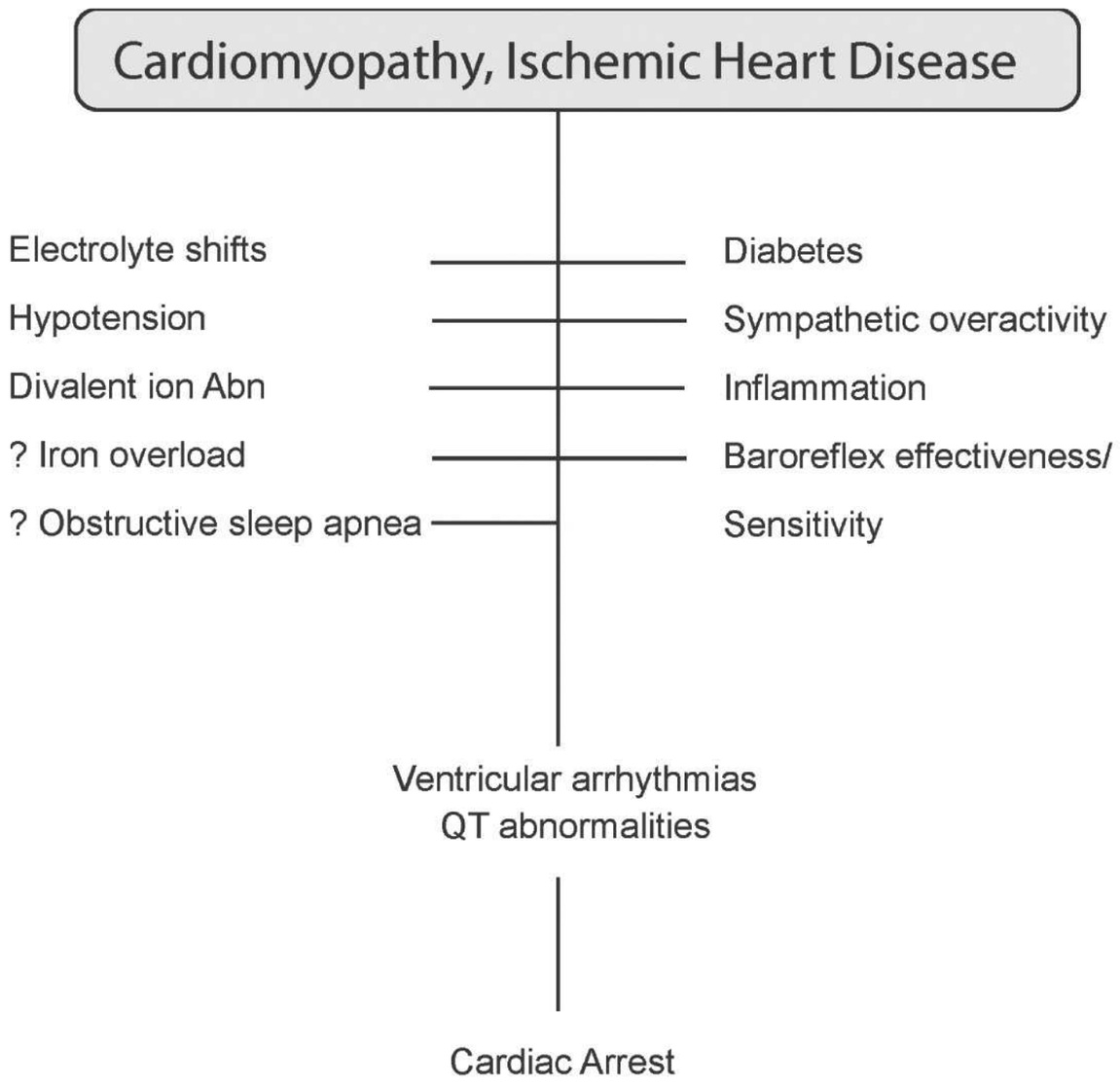

FIGURE 79.6 The mechanisms of sudden cardiac death in chronic kidney disease.

contribute to the risk of sudden death. Each of these risk factors is discussed in greater detail in the following.

Prolonged corrected QT (QTc) intervals in patients with CKD and ESRD usually result from inhomogeneity of both myocardial depolarization and repolarization that occurs secondary to LVH and intercardiomyocytic fibrosis. Measures of the temporal variability in myocardial repolarization include QT dispersion and QT variability index. The former is defined as the difference between the maximal and minimal QT intervals on a standard ECG (QTmax – QTmin) and is associated with an increased risk of ventricular arrhythmias and mortality in patients with congestive heart failure and in the general population.[153] The latter is calculated as the logarithm of the ratio between the variances of the normalized QT and RR intervals. It can predict the subsequent risk of sudden cardiac death or ventricular arrhythmia in patients who present for electrophysiologic investigation.[154]

Left ventricular hypertrophy. LVH could predispose individuals to sudden death through the prolongation of the QTc interval or by increasing arrhythmogenesis. The QTc interval is substantially longer in hemodialysis patients than in those who have near normal kidney function, and is associated with several manifestations of uremic cardiomyopathy, including increased LV mass index and end-diastolic volume, and a reduced LV ejection fraction.[155] In addition, more premature ventricular complexes (PVCs) occur during hemodialysis in patients with LVH compared with those without LVH.[138]

Ischemic heart disease. In the general population, coronary heart disease is an important cause of sudden death. In patients undergoing hemodialysis, CAD probably causes arrhythmogenesis because severe coronary stenosis is associated with the induction and lengthy persistence of ventricular arrhythmias during and after hemodialysis.[156] Furthermore, the number of PVCs during and after hemodialysis is higher in patients with ischemic heart disease than in those without it.[138,156]

Novel markers of coronary ischemia can identify patients who are at a high risk of cardiac death. Ischemia modified albumin (IMA) is a novel biomarker of acute ischemia that has high sensitivity and moderate specificity.[157,158] In 114 patients with ESRD, an IMA level of 95 KU per liter predicted all-cause mortality with a sensitivity and specificity of 76% and 74%, respectively, whereas an elevated cardiac troponin level ≥ 0.06 μg per liter predicted mortality with a sensitivity of 75% and a specificity of 72%.[159] Cardiac mortality risk was increased sevenfold in patients with combined elevated IMA and cardiac troponin levels (odds ratio [OR] = 7.12; 95% CI, 4.14 to 10.12).

QT dispersion and variability. Elevated QT dispersion was evident in 20 hemodialysis patients and 20 patients treated with continuous ambulatory peritoneal dialysis, and was significantly higher than in healthy controls.[160] The difference in QT dispersion rates between patients undergoing hemodialysis and those on chronic ambulatory peritonial dialysis (CAPD) was not statistically significant. In a retrospective cohort study of 147 adult patients undergoing dialysis, a QTc interval dispersion that occurred for longer than 74 ms was an independent predictor of all-cause mortality (relative risk [RR], 1.5; 95% CI, 1.2 to 2.0), and of cardiovascular mortality (RR, 1.6; 95% CI, 1.2 to 2.4).[161]

The QT variability index was increased by 47% in 163 patients with advanced CKD (43 individuals with stage

4 CKD, 67 patients undergoing hemodialysis, and 43 patients on CAPD) during a 30-minute rest period compared with 39 age-matched healthy controls.[162] The variability index was similar in patients with stage 4 CKD and in those on dialysis, whereas it was higher in patients with diabetes compared with nondiabetic patients with renal failure. Furthermore, in a multiple linear regression analysis, a history of diabetes or CAD were the only independent predictors of the QT variability index in patients with advanced CKD. The elevated index in patients with advanced CKD was the result of both reduced RR interval variance (secondary to reduced autonomic control of heart rate) and increased QT interval variance.[162]

It should be noted that several drugs (such as typical and atypical antipsychotics, sotalol, and antiarrhythmic agents) could prolong cardiac repolarization (QT interval) and trigger torsades de pointes, and could increase the risk of sudden cardiac death in patients with CKD.[163]

Baroreflex effectiveness and sensitivity. Impaired arterial baroreflex function is associated with an increased risk of ventricular arrhythmia and sudden cardiac death.[164] In healthy individuals, an appropriate baroreflex response is usually obtained in 25% of all systolic BP ramps during the day and in 15% of ramps during the night.[165] The ability of the arterial baroreflex to preserve short-term BP homeostasis—defined as arterial baroreflex sensitivity—has been identified as a prognostic marker of cardiovascular mortality in patients with MI.[166] The baroreflex effectiveness index is defined as the ratio between the number of systolic BP ramps, followed by baroreflex-mediated changes in heart rate, and the total number of systolic BP ramps during the recording period.[167]

In 216 patients with hypertension and stage 4 or 5 CKD, the baroreflex sensitivity was reduced by 51% and the baroreflex effectiveness index was reduced by 49% compared with age-matched healthy controls (n = 43).[164] Although the treatment modality for renal failure had no effect on baroreflex sensitivity or effectiveness, patients with CKD and diabetes had a greater reduction in both baroreflex sensitivity and effectiveness than patients with CKD who did not have diabetes. During the 41-month follow-up period, 69 patients with hypertension died.[167] Sudden cardiac death occurred in 15 of these patients (22% of all deaths). The reduced baroreflex effectiveness index was an independent predictor of all-cause mortality, whereas reduced baroreflex sensitivity was an independent predictor of sudden cardiac death.[167]

Inflammation. Inflammation has been associated with sudden cardiac death independently of traditional cardiovascular risk factors.[168] After adjusting for demographic characteristics, comorbidities, and laboratory factors, the highest tertiles of the inflammatory markers C-reactive protein (CRP) and interleukin 6 (IL-6) were associated with a doubled risk of sudden cardiac death compared with the lowest tertiles, whereas a decrease in serum albumin level was associated with a 1.35-fold increased risk of sudden cardiac death in the highest tertile compared with the lowest tertile.[169] Inflammation could trigger sudden cardiac death through premature atherosclerosis and cytokine-induced plaque instability or by a direct effect on the myocardium and the electrical conduction system.

Impact of the hemodialysis prescription. A rapid change in the extracellular concentration of electrolytes during a dialysis session leads to a secondary shift of electrolytes between the intracellular and extracellular milieu, which depends on the electrochemical gradient. As a result, cellular membrane polarization and stability may be affected. Data from patients treated at Fresenius Medical Care North America–affiliated centers showed that dialysis with a potassium dialysate concentration of zero or 1 mmol per liter was a significant risk factor for cardiac arrest.[149] This prescription had been used in 17.1% of patients who experienced a cardiac arrest compared with 8.8% of controls ($P < .0001$).[149] Cardiac arrests were more frequent during dialysis sessions carried out on a Monday as compared to Wednesday ($P = .001$) and Friday ($P = .004$). Although the mechanism for this observation was not studied, it may be due to increased fluctuations in potassium concentrations or perhaps increased ultrafiltration volumes.

Further evidence to support modifiable risk factors associated with the hemodialysis prescription causing sudden cardiac arrest has been reported recently. From the DaVita/Gambro Healthcare database of 43,200 outpatient dialysis patients, 502 patients who experienced a sudden cardiac arrest were compared to 1,632 age-and dialysis vintage–matched controls.[169] Independent factors associated with sudden cardiac arrest included low potassium dialysate < 2 mEq per liter, increased ultrafiltration volume, exposure to low calcium dialysate, and low serum creatinine levels. This study suggests that modification of the hemodialysis prescription may reduce the risk of sudden cardiac arrest, although the case-control research design is of low evidentiary power.

Evidence to support increased ultrafiltration volume as a CV risk factor was reported in a cohort of 1,846 patients. Rates over 13 mL/hr/kg, compared to ultrafiltration rates up to 10 mL/hr/kg, were significantly associated with all-cause and CV-related mortality (adjusted hazard ratio = 1.59 and 1.71, respectively).[170] In the subset of patients with congestive heart failure, ultrafiltration rates between 10 and 13 mL/hr/kg were also significantly associated with all-cause mortality.

In addition to low potassium dialysate, a decreasing potassium profile during hemodialysis may be harmful; complex arrhythmias were observed more frequently during and after hemodialysis in those with a decreasing potassium profile compared with individuals whose potassium levels were kept constant (2.5 mmol per liter).[171]

Abnormalities in calcium homeostasis may also be cardiotoxic. In 68 nondiabetic patients with ESRD who were undergoing hemodialysis with a normal maximal ECG stress test and no evidence of LVH on ECG, hemodialysis increased QTc intervals from 421 ± 26 ms before hemodialysis to 434 ± 29 ms after hemodialysis ($P = .005$).[172] Abnormally prolonged QTc intervals (> 440 ms) after hemodialysis were

recorded 1.5 to 2.3 times more often than in the high-risk diabetic population. In addition, patients with greater increases in QTc intervals after hemodialysis had higher baseline plasma calcium levels ($r = 0.47$; $P < .001$), and lower calcium levels after hemodialysis ($r = 0.33$; $P < .05$). These data suggest that abnormalities in calcium hemostasis may induce the prolongation of QTc, and thus may predispose a patient to sudden death.

Drugs. In a large, retrospective study of 43,200 patients undergoing hemodialysis, 729 patients experienced a cardiac arrest.[173] β-Blockers were prescribed more frequently among those who survived than among those who died from a sudden cardiac arrest (53% versus 40%; OR, 0.59; 95% CI, 0.43 to 0.80). Among those who survived, β-blockers were associated with a significantly lower risk of death at 24 hours and 6 months after cardiac arrest. In addition, a positive correlation was observed between increasing β-blocker dose and survival. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) was associated with a significantly reduced risk of sudden cardiac death after 6 months of treatment (adjusted OR, 0.51; 95% CI, 0.28 to 0.95; $P = .03$) in survivors of a cardiac arrest.[173] A positive correlation was observed between the dose of ACE inhibitor and/or ARB and survival. Selection bias in the treatment group could, however, potentiate the positive effect of β-blockers on survival, because patients with very poor cardiac function, low BP, and/or intradialytic hypotension might not be prescribed these drugs.

All Cause Mortality

Incident cardiac events. The severity of CKD portends a worse prognosis if a cardiac event occurs. A study of 3,106 patients with MI reported an in-hospital mortality of 2% for patients with normal renal function, 6% for mild CKD, 14% for moderate CKD, 21% for severe CKD, and 30% for patients dependent on dialysis.[174] A meta-analysis of trials of thrombosis for MI indicated an inverse correlation between GFR and mortality at 1 month.[175]

In a large prospective register of nearly 50,000 cases of ST-segment elevation MI and non–ST-segment elevation infarction, the prevalence of CKD was high: 30% in the former group and over 40% in the latter.[176] Cases with CKD had a greater prevalence of diabetes, hypertension, and prior CVD than those without CKD. Even in patients with early stage 3 CKD, the risk of short-term mortality after acute coronary syndrome was twofold higher than in those without CKD. Patients with CKD were less likely to undergo invasive therapies, and had lower rates of β-blocker and statin use.

CKD is an important predictor of mortality risk in patients with CHF.[177,178] In a secondary analysis of the Digoxin Intervention Group trial, Shlipak et al.[179] found that patients with stable CHF and an ejection fraction less than 45% had a higher risk of death with a GFR ≤ 50 mL per minute (HR, 2.6; 95% CI, 1.69 to 2.51). Patients with a GFR of 50 to 60 mL per minute had no increase in mortality relative to the patients with better renal function.

Baseline cardiomyopathy. The presence of concentric LVH, LV dilation with normal contractility, and systolic dysfunction at the time of ESRD therapy initiation has been associated with progressively worse survival, independent of age, sex, diabetes, and IHD.[126] In a study of CKD stage 3/4 patients CV event-free survival was significantly worse in the presence of concentric and eccentric LVH compared with the absence of LVH.[123]

Excessive hypertrophy in concentric LVH (high LV mass to volume ratio) and inadequate hypertrophy in LV dilation (low LV mass to volume ratio) were independently associated with late mortality in a Canadian dialysis cohort.[18] However, in 596 incident hemodialysis patients, an adjusted association between baseline LV mass index and subsequent CV events or death was eliminated by adjusting for age, diabetes, systolic BP, and N-terminal pro-B type natriuretic peptide.[19]

Among renal transplant recipients, LVH at the time of transplantation was an independent risk factor for death (RR, 1.9; 95% CI, 1.22 to 3.22) and CHF (RR, 2.27; 95% CI, 1.08 to 4.81) in the subsequent 5 years.[180]

In a Japanese study of 1,254 consecutive incident hemodialysis patients, 8.5% had an LV ejection fraction of 40% to 50%, 3.3% had an ejection fraction of 30% to 40%, and 1.4% had an ejection fraction < 30%. Seven year event-free survival for the respective groups was 57%, 46%, and 23%, respectively, as compared to about 67% in the group with an ejection fraction above 50%. After adjusting for other risk factors, a decreasing ejection fraction was a strong independent predictor for CV death.[181]

Sixty-four percent of 70 prevalent HD patients had significant myocardial stunning during hemodialysis.[182] A significantly increased hazard of death occurred in those with myocardial stunning and elevated cardiac troponin T than in those with elevated levels alone. The LV ejection fraction at rest fell from 62% at baseline to 55% after 12 months in those with regional wall motion abnormalities compared to a fall from 60% to 56% in those without regional wall motion abnormalities.

Baseline calcification. In a prospective study of 117 nondialyzed Brazilian patients with CKD, the presence of coronary artery calcification was significantly associated with the subsequent occurrence of CV events independent of age and diabetes.[183]

Recently, 1,084 prevalent dialysis patients had scoring of abdominal aortic calcification using plain lateral abdominal X-rays and measurements of carotid femoral PWVs, and were followed for 2 years.[184] Compared with the lowest tertile of aortic calcification, the risk of a CV event was increased by a factor of 3.7 in patients with a score in the middle tertile, and by a factor of 8.6 in the highest tertile. The risk associated with an increased PWV was less pronounced at higher levels of calcification. After accounting for

age, diabetes, and serum albumin, both aortic calcification and PWV were independent predictors of outcome.

Among 140 patients with ESRD who underwent ECG and coronary angiography, 56 (40%) had mitral annular calcifications, which was associated with a significant increase in all-cause mortality ($P = .04$).[92] Mitral annular calcification was also independently associated with substantial CAD, defined as luminal stenosis > 70% by visual estimation in at least one coronary artery (OR, 12; 95% CI, 3.3 to 26.1).

Baseline symptomatic cardiac disease. In a Canadian prospective cohort study, patients with clinical IHD at the start of dialysis were more likely to have an admission for CHF (RR, 1.7) or to die (RR, 1.5) than patients free of IHD at baseline, after adjusting for age and diabetes.[132] In these patients, most of the excess mortality associated with IHD seemed to be through the development of CHF. In diabetic renal transplants, the presence of IHD was associated with a fourfold risk of future events and death.[185]

For dialysis patients, CHF has a poor prognosis; the median survival of patients who had heart failure at or before the initiation of ESRD therapy was 36 months, compared with 62 months in subjects without baseline CHF.[15] This adverse prognosis was independent of age, diabetes, and IHD. Among patients who had heart failure at baseline, recurrent heart failure developed in 56% and the remaining 44% were failure free during follow-up. Median survival in those with recurrent CHF was 29 months, which was significantly less than in those without recurrence (45 months). For RTRs, the development of new onset CHF carries a prognosis similar to that for new IHD (RR for death, 1.78; 95% CI, 1.21 to 2.61 for CHF versus RR for death, 1.50; 95% CI, 1.05 to 2.13 for IHD).[13]

Risk Factors

Although experimental studies in animal models and cross-sectional or case-control studies in small groups of patients can lend insights into the mechanisms of disease in renal failure, only large, rigorous, prospective studies in relevant clinical populations (free of cardiac disease at baseline), can identify widely generalizable risk factors for CVD. The Framingham Study is the archetypal population-based cohort study in the field of CVD, and the risk factors identified by it have been widely vindicated in subsequent intervention trials on BP control and cholesterol reduction. Unfortunately, few large, adequately designed prospective cohort studies on CV outcomes have been performed in renal failure populations. We await with interest the results of the large Chronic Renal Insufficiency Cohort (CRIC) study ongoing in the United States, which should be powered enough to identify the most important independent risk factors for CV events.[186]

Table 79.2 outlines independent predictors of cardiac events identified by studies such as ARIC in CKD,[8,131,187] the Canadian cohort of incident dialysis patients all of whom had echocardiography at baseline,[15,125–128,132,188–191] the U.S. incident cohort of dialysis patients enrolled in CHOICE,[192–194] the 4D study of prevalent diabetic hemodialysis patients,[195–201] the Canadian incident renal transplant cohort,[13,180] and others. Whether these predictors of CV risk can be modified by risk factor intervention is also summarized in Table 79.2.

Nonmodifiable Risk Factors

Age. Older age has been independently associated with the occurrence of coronary events[131] and with the development or worsening of CVD in the CKD population.[202,203] Among dialysis patients, older age is predictive of the de novo occurrence of angina pectoris, MI, or coronary revascularization[132] and of de novo heart failure.[15] Among renal transplant recipients, age is an independent risk factor for MI or coronary revascularization or death from MI[130] and the development of de novo heart failure.[13]

Gender. Gender is an inconsistent predictor of CV events in CKD, although male gender was associated with coronary events in CKD,[131] and female gender with ischemic heart disease events in renal transplant recipients.[13]

Diabetes mellitus. Almost half the cases of ESRD are caused by diabetes mellitus, particularly type 2.[151] Diabetes confers a substantially increased risk of coronary events in CKD patients (Table 79.1).[131] On starting dialysis, diabetics had more concentric LVH, IHD, and cardiac failure than nondiabetic patients.[191] Among patients on dialysis, diabetes is independently associated with the development of de novo IHD but not with de novo heart failure (Table 79.3A).[191] In renal transplant recipients, diabetes was associated with de novo ischemic heart disease and heart failure events (Table 79.3B).[13] In another study of renal transplant recipients, diabetes was strongly associated with multiple atherosclerotic outcomes (RR of 2.09 for MI, revascularization, or death from MI; RR of 2.98 for ischemic stroke; and RR of 25.7 for development of peripheral vascular disease).[130]

The impact of diabetes in all renal populations may well be underestimated. Angiographic studies in asymptomatic diabetic patients on dialysis show that approximately one-third have at least one coronary artery stenosis of 50% or greater.[93] Among asymptomatic diabetic patients referred for renal transplantation, 88% of those older than 45 years had significant coronary stenosis.[185]

There is evidence for a specific diabetic cardiomyopathy in diabetic patients without ESRD.[204,205] Furthermore, LVH, along with cardiac fibrosis, is a more frequent finding in hypertensive diabetic patients than in hypertensive nondiabetic patients.[84]

Modifiable Traditional Risk Factors

Hypertension

Predictor of CV events. The primary cause of ESRD in the United States is hypertension (27% of cases).[151] Furthermore, CKD, whatever its cause, is usually associated with hypertension. In the Modification of Diet in Renal Disease (MDRD) Study, although 91% of CKD patients were treated

79.2 Traditional and Nontraditional Modifiable High-risk Factors for Cardiovascular Disease in Chronic Kidney Disease: Evidence from Cohort Studies and Randomized Controlled Trials

	Cohort		RCT	
	CKD	Dialysis	CKD	Dialysis
Traditional				
Hypertension	+	+	+	?
Smoking	+	+	NA	NA
Hyperlipidemia	+	+	+	−/+
Hyperglycemia	+	+	ND	ND
Obesity	+	+	ND	ND
Nontraditional				
Moderate anemia	+	+	−	−
Hypoalbuminemia	+	+	ND	ND
Inflammation	+	+	ND	ND
Hyperfibrinogenemia	+	+	+	+
Troponin	?	+	ND	ND
Oxidant stress	ND	ND	−	+
Hyperhomocysteinemia	+	+	−	IP
Hyperphosphatemia	+	+	ND	ND
Hyperparathyroidism	ND	+	ND	IP
Degree of renal impairment	+	NA	+	NA
Mode of dialysis	NA	+	NA	+
Salt + H_2O overload	+	+	ND	?
A-V fistula/graft	NA	−	NA	+

CKD, chronic kidney disease; RCT, randomized controlled trial; +, positive; –, negative; ND, not done; NA, not applicable; IP, in progress; A-V, arterio-venous.

with antihypertensive agents, only 54% had BPs of 140/90 mm Hg or less.[206] Hypertension is present in 86% of U.S. dialysis patients, yet it is adequately controlled in only 30% of cases.[207] In the ARIC Study, hypertension substantially increased the risk of coronary heart disease (Table 79.1).[131] Hypertension has been shown to promote LV growth in a large cohort of patients with CKD[124] and its control may prevent or regress LVH.[208,209]

In patients on dialysis, each 10 mm Hg increment in BP is associated with a 48% higher risk for the development of LVH.[188] Furthermore, higher systolic BP over time was an independent predictor for progressive LVH.[19] Hypertension is an independent predictor of de novo heart failure and of de novo IHD events in incident dialysis patients (Table 79.3A).[188]

After transplantation, hypertension was associated with the progression to LVH in patients with normal hearts

79.3 Predictors of De Novo Cardiovascular Events in Incident Dialysis Patients[15,132] and in Incident Transplant Recipients[13]

A. Dialysis Patients	Heart Failure		MI/Angina	
(n = 432)	HR	P	HR	P
Diabetes		NS	3.2	0.0002
Hypertension per 10 mm Hg rise in SBP	1.44	0.007	1.39	0.05
Anemia per 1 g/dL decrease	1.28	0.02		NS
Hypoalbuminemia per 10 g/L fall	1.30	0.007	1.49	< 0.001
B. Transplant Recipients[a]	**Heart Failure**		**MI/Angina**	
(n = 638)	HR	95% CI	HR	95% CI
Diabetes	2.30	1.4–3.7	2.4	1.5–3.9
Hypertension per 10 mm Hg rise in SBP	1.29	1.1–1.5	1.41	1.0–1.9
Anemia per 10 g/L decrease	1.24	1.1–4.1		NS
Hypoalbuminemia per 10 g/L fall	2.10	1.1–4.1		NS

[a]Alive and free of clinical heart disease at 1 year.
HR, hazard ratio; MI, myocardial infarction; CI, confidence interval; SBP, systolic blood pressure; NS, not stated.

at transplantation.[210] A prospective cohort study demonstrated that diastolic BP was an independent risk factor for increasing LV mass between the first and fifth years after transplantation, but systolic BP was the only predictor of de novo LVH at 5 years.[180] Hypertension was also an independent risk factor for cardiac events in renal transplant recipients (Table 79.3B).[13]

Despite these strong data substantiating hypertension as a predictor of CV events in CKD, there is a U-shaped curve association of BP and mortality in hemodialysis patients,[211,212] with lower BP predicting higher mortality. However, the high prevalence of cardiac disease at the start of ESRD therapy is a confounding issue even for well-executed, prospective cohort studies. Because cardiac dysfunction can cause low BP and is independently associated with death, even prospective studies cannot exclude the possibility that low BP is simply a surrogate marker for poor pump function, unless patients with cardiac abnormalities at baseline are excluded from analysis. This is difficult to do in practice because most patients (75% to 80%) have ECG abnormalities at the start of maintenance dialysis.[125] In one prospective cohort study[188] of 433 patients on dialysis, high BP was positively associated with the development of de novo heart failure, which in turn was associated with both a drop in mean arterial pressure and subsequent death. These observations suggest, but do not prove, the following causal sequence:

Hypertension → IHD and LVH → Pump failure → hypotension and death

This chain of events is supported by the changing relationship of BP with mortality over time in 16,959 incident dialysis patients.[213] For those with systolic BP < 120 mm Hg, increased mortality was observed in the first 2 years after the initiation of dialysis, whereas in those with systolic BP ≥ 150 mm Hg, increased mortality was observed after year 2. Using time-varying analyses, mild-to-moderate hypertension was relatively well tolerated. Furthermore, in an incident cohort of hemodialysis patients without symptomatic cardiac disease at baseline, hypertension was an independent predictor of CV events during 2 years of follow-up.[19]

Treatment in CKD patients. Control of BP in predialysis CKD is probably best undertaken by the normalization of blood volume and the use of inhibitors/blockers of the renin-angiotensin system. The use of ACE inhibitors or ARBs are considered the agents of first choice in most patients due to their documented benefit in delaying the progression of CKD in both diabetic and nondiabetic disease, particularly with associated proteinuria.[214] Ramipril has improved CVD outcomes in patients with decreased GFR and at least one CVD risk factor, in addition to either diabetes or manifest vascular disease.[2] The ARB, losartan, has reduced hospitalization for heart failure in diabetics with overt nephropathy.[215] In 1,715 adults with diabetic nephropathy, irbesartan (another ARB) significantly reduced the incidence of CHF compared to placebo (HR = 0.72; 95% CI, 0.52 to 1.0).[216] It appears that the beneficial impact of blockade of the renin-angiotensin system is more than can be accounted for by lowering of BP.

An analysis of the achieved BP in the Irbesartan Diabetic Nephropathy Trial (N = 17.5) demonstrated that the progressive lowering of systolic BP to 120 mm Hg was associated with renal protection and decrement in mortality and CV events.[217] However, with systolic BP < 120 mm Hg, renal protection was observed but there was an increase in all-cause mortality, CV mortality, and CHF in patients who have a more severe underlying cardiac disease. Assignment to irbesartan lowered the risk for heart failure by 29%, lowering the systolic BP by 20 mm Hg did so by 25%, and the combination of both lowered the risk by 53%.

Management of hypertension should generally aim for levels less than 130/80 mm Hg for CKD, particularly in those with ≥ 1 g per day of proteinuria.[218] In some patients, particularly diabetics with moderate-to-advanced renal dysfunction, BP can be highly resistant to intervention, requiring extensive combination treatment. However, this Kidney Disease Outcomes Quality Initiative (KDOQI) target BP was driven by observational data or secondary analyses from RCTs.[218] Results of RCTs establishing the benefits or harm in meeting a goal BP < 130/80 mm Hg in CKD patients are necessary because no primary analysis of any RCT supports lower BP goals.[219] In the interim, individualization of therapy is recommended.

In renal transplant recipients, calcium channel blockers (CCBs) are widely used because they are well tolerated and because of their effects in counteracting calcineurin-mediated vasoconstriction. The use of ACE inhibitors or ARBs is probably justified in most patients, particularly because the regression of LVH has been reported in renal transplant recipients with ARBs. However, issues relating to hyperkalemia, anemia, and a reduction in eGFR warrant consideration, particularly in the first 12 months posttransplantation.

Treatment in dialysis patients. The mainstay of therapy in dialysis patients is the maintenance of normal extracellular fluid volume, as suggested by the results of a dialysis regimen of long, slow ultrafiltration, which was associated with normotension, regression of LV hypertrophy, and improved survival.[220] In a RCT of hypertensive patients on hemodialysis, 100 patients were assigned to receive ultrafiltration, prescribed as an additional weight loss of 0.1 kg per 10 kg of body weight per dialysis above that which is required to remove interdialytic fluid gain. There were 50 patients assigned to the control group.[221] At 4 weeks, a mean reduction in postdialysis weight of 0.9 kg was achieved, which resulted in significant improvements in BP (7 mm Hg in systolic and 3 mm Hg in diastolic). This demonstrates that extracellular volume expansion, even in the absence of clinical signs of volume overload, mediates, at least in part, hypertension in hemodialysis patients.

RCTs of the CV effects of ACE inhibitors or ARBs in hemodialysis are few in number, consist of few patients, and are of variable quality.

London and colleagues[222] compared the effects of an ACE inhibitor (perindopril) with a CCB (nitrendipine) in a double-blinded, randomized trial involving 24 hemodialysis patients with LVH over a period of 12 months. At baseline, each group displayed LVH due predominantly to an increased LV end-diastolic diameter. Similar and significant changes were found in BP, total peripheral resistance, aortic and arterial PWVs, and arterial wave reflections. After treatment, there was a significant decrease in LV mass in the perindopril-treated group only. It was also found that LV mass reductions were related not to changes in LV wall thickness but rather to a reduction in LV end-diastolic diameter.

The FOSIDIAL study,[223] a placebo-controlled randomized trial of prevalent hemodialysis patients with established LVH, did not show a substantial adjusted effect of the ACE inhibitor fosinopril on the primary end point (the combined fatal and nonfatal first cardiovascular events) in the intention to treat analysis (RR, 0.93; 95% CI, 0.68 to 1.26) or in the per protocol analysis (adjusted RR, 0.79; 95% CI, 0.59 to 1.10). However, this study was underpowered for the primary event rate. Furthermore, patients assigned to the treatment group had a higher baseline risk (such as LVH, CAD, diabetes, and duration on hemodialysis) than the control group.

In a small randomized controlled trial of 80 patients undergoing hemodialysis, who had no clinical evidence of cardiac disease, use of the angiotensin II type I–receptor blocker, candesartan, was associated with a reduced incidence of CV events and mortality compared with placebo: 46.3% versus 53.8%.[224]

A meta-analysis (5 RCTs) of ACE inhibitor and ARB use resulted in a statistically significant reduction in LV mass, with a weighted mean difference compared to controls of 15.4 g per square meter (95% CI, 7.4 to 23.3).[225] In 3 RCTs, the relative risk of CV events associated with ACE inhibitor or ARB use was 0.66, but the 95% CIs were 0.35 to 1.25.

A cohort of patients was examined for the effects of BP changes on 150 dialysis patients over a mean of 51 months.[49] Independent predictors of CV mortality included no reduction in PWV in response to a BP decrease (RR, 2.59; 95% CI, 1.51 to 4.43), an increased LV mass (RR, 1.11 per 10 g increase in LV mass index, 95% CI, 1.03 to 1.19), age (RR, 1.69; 95% CI, 1.32 to 2.17), preexisting CVD, and lack of ACE inhibitor treatment (RR, 0.19; 95% CI, 0.14 to 0.43). These findings were consistent with earlier descriptive studies, but for the first time suggested that there might be a survival advantage in reducing PWV. Importantly, ACE inhibitors appeared also to have a favorable effect on survival in this patient group, which was independent of BP change.

A reasonable target BP for antihypertensive treatment is a predialysis BP < 140/90 mm Hg, unless the patient develops symptomatic hypotension or low BP during or after dialysis. Patients with a BP > 140/90 mm Hg after achievement of their base day weight should have antihypertensive drugs prescribed.

The selection of antihypertensive agents is best guided by the presence of associated comorbidities. There are not, however, large randomized trials to support one agent over another. Hence, patients with reduced LV systolic function are likely to benefit from ACE inhibitors or ARBs, and patients

with relatively intact LV function postmyocardial infarction should be treated with a β-receptor antagonist. Practical difficulties in this patient group in particular include associated cerebrovascular or coronary disease, advanced age, and CV instability in relation to ultrafiltration. In such situations, BP will require individual targeting and some compromise on the optimal target will be necessary.

Smoking

Predictor of cardiovascular events. Although 25% of patients with CKD were current or former smokers as of 2001,[226] the prevalence of current smokers is probably decreasing. In a recent RCT[227] only 5% were current smokers, although 40% were previous smokers.

The Cardiovascular Health Study[228] investigated 5,808 people who had CKD and were ≥ 65 years, and observed 20 extra deaths per 1,000 patient years in current smokers. In the ARIC population-based study of CKD patients,[131] the relative risk for coronary disease was 1.91 in current smokers (Table 79.1). Smoking has been independently associated with subsequent de novo heart failure, peripheral vascular disease, and death at the start of dialysis.[14] Among renal transplant recipients, a smoking exposure has been independently associated with ischemic stroke, peripheral vascular disease, and death.[229]

Intervention. RCTs are not necessary to demonstrate that cessation of smoking is beneficial. However, in renal transplant patients, most continued to smoke after transplantation despite admonitions to quit.[230]

Obesity. Obesity is an independent predictor of coronary events in CKD (Table 79.1),[131] but there is no evidence to suggest it is an independent risk factor in patients on any type of dialysis.

Hyperlipidemia

Predictor of cardiovascular events. An atherogenic lipid profile is highly prevalent in patients with renal disease, particularly in patients with nephrotic syndrome.[231] In CKD, hypercholesterolemia and hyperapolipoproteinuria B are independent predictors of coronary disease (Table 79.1).[131] The prevalence of dyslipidemias in renal transplant recipients is high. Hypercholesterolemia has been linked to ischemic events in this population.[130,133]

In dialysis patients, the highest mortality risk appears to be associated with low, not high serum cholesterol.[232] This may be because low total cholesterol is strongly correlated with poor nutritional status, inflammation, and low albumin levels, which are themselves associated with increased mortality risk. In CHOICE,[193] a prospective study of patients starting dialysis, high serum cholesterol was associated with low all-cause mortality risk in the presence of inflammation, but with increased risk in individuals without inflammation (HR, 1.32 per 1.0 mmol per liter increment in total cholesterol; 95% CI, 1.07 to 1.63). This supports the hypothesis that the inverse association of total cholesterol level with mortality in dialysis patients is likely due to the cholesterol-lowering effect of systemic inflammation and malnutrition, not to a protective effect of high cholesterol concentrations.

In stage 3 and 4 CKD, the presence of malnutrition/inflammation also modified the relationship of serum cholesterol with CVD. African Americans with hypertensive CKD were stratified using body mass index (BMI) < 23 kg per square meter or C-reactive protein > 10 mg per deciliter. In the group without evidence of malnutrition/inflammation, the adjusted cholesterol HR increased progressively across cholesterol level, but in those with malnutrition/inflammation, the HRs did not vary significantly by cholesterol level.[233]

Although lipoprotein (a) is elevated in patients on dialysis and is independently associated with IHD and death,[234] its clinical utility as a test is limited.

Intervention. The data on the efficacy of statin (HMG coenzyme A [CoA] inhibitor) therapy in CKD arises from RCTs in patients with or at high risk of coronary disease, and CKD patients are clearly at the highest risk of atherosclerotic events. Tonelli et al.[235] performed a secondary analysis of a subset of patients with a GFR of 30 to 60 mL per minute from three randomized trials of pravastatin versus placebo. Among the 4,491 subjects identified, pravastatin significantly reduced the incidence of MI, coronary death, or coronary revascularization (HR, 0.77; 95% CI, 0.68 to 0.86), which is similar to the effect of pravastatin on the primary outcome in subjects with normal function (HR, 0.78; 95% CI, 0.65 to 0.94).[235] A pooled analysis of 30 completed RCTs investigating the effect of fluvastatin in patients with creatinine clearance < 50 mL per minute demonstrated a 41% reduction in combined cardiac death and MI compared to placebo.[236]

These results were not replicated in three RCTs in ESRD populations. An RCT in renal transplant recipients of fluvastatin (40 to 80 mg per day) in 2,102 RTRs failed to find a benefit with respect to primary composite cardiac end points (MI, cardiac death, and cardiac intervention). Post hoc analysis using alternative outcomes suggested that fluvastatin reduced the incidence of cardiac death or definite MI from 104 to 70 events (RR, 0.65; 95% CI, 0.48 to 0.88).[237] The 4D Study, a randomized trial of atorvastatin versus placebo in type 2 diabetics who had been on hemodialysis for no more than 2 years, demonstrated no reduction in the rate of CV mortality and of nonfatal MI compared to placebo.[195] The AURORA study,[238] an RCT of rosuvastatin in hemodialysis patients who had low-density lipoprotein (LDL) cholesterol of 2.6 mmol per liter at baseline, revealed no difference in primary event rate (cardiovascular death, nonfatal MI, or stroke) in the rosuvastatin-treated group compared to placebo. This trial was probably underpowered to answer the research question, patients already on statins were excluded (which probably amounted to 40% of the hemodialysis population), and discontinuation of the assigned treatment occurred in about half of the enrolled patients, all of which limit the conclusions that can be made.

The disappointing results of 4D and AURORA have been recently countered by the results from the Study of Heart and Renal Protection (SHARP)[239] where 9,438 CKD patients (3,191 on dialysis and 6,247 not on dialysis) with no history of MI or coronary revascularization were randomly allocated to lipid lowering agents ezetimibe/simvastatin or placebo. During median follow-up of 4.9 years, major atherosclerotic events occurred significantly less frequently in the ezetimibe/simvastatin group compared to placebo (RR, 0.83; 95% CI, 0.74 to 0.94), with similar reductions observed in both dialysis and nondialysis patients.

Because of the benefit of statins that were demonstrated in predialysis CKD and in SHARP, together with the clear benefit observed in the general population, it seems reasonable to treat CKD patients in a similar manner, provided their life expectancy is such as to benefit from these drugs. The KDOQI guidelines for managing dyslipidemia in CKD recommend that patients with CKD should be considered in the highest risk group for CV events.[240] Thus LDL cholesterol levels of 100 mg per deciliter (2.56 mmol per liter) or more and 130 mg per deciliter (3.33 mmol per liter) or more are treatment thresholds for diet and drug therapy, respectively. Drug therapy is recommended if LDL cholesterol levels remain in the range of 100 to 129 mg per deciliter despite 3 months of lifestyle changes. The target LDL level is 100 mg per deciliter (2.56 mmol per liter) or less. A cholesterol-lowering diet should be part of the treatment program, but most patients require pharmacologic therapy. For patients with high LDL levels, statins are recommended as first-line therapy. These agents are safe and effective in uremic patients, but screening for myositis should be undertaken. Fibrates are also effective in CKD patients, but dose reduction appropriate to the level of renal failure is important. The combination of a statin and a fibrate is associated with a high risk of muscle toxicity and in general should be avoided. The KDOQI guidelines suggest that fibrates may be used either for patients with triglyceride levels greater than 500 mg per deciliter or statin-intolerant patients who have triglycerides greater than 200 mg per deciliter with non-high-density lipoprotein (HDL) cholesterol > 130 mg per deciliter. Similar guidelines have been published for the renal transplant population.[241]

Hyperglycemia

In addition to the presence of diabetes mellitus, hyperglycemia is an independent risk factor for the development of CAD in CKD (Table 79.1).[131] In the 4D study of prevalent diabetic hemodialysis patients, poor glycemic control was strongly associated with sudden cardiac death, which accounted for increased CV events and mortality.[196] In contrast, the rate of MI was not affected. However, in another study, higher glucose and HbA1C levels were not associated with mortality in 1,484 incident hemodialysis patients with and without diabetes.[242] Whether interventions to achieve tighter glycemic control will improve cardiac outcomes in CKD is unknown.

Uremia-Related Risk Factors

Anemia

Predictor of cardiovascular events. Anemia is a predictor of CAD in CKD (Table 79.1),[131] of the development of de novo cardiac failure in dialysis (Table 79.3A),[15] and of de novo heart failure in renal transplant recipients (Table 79.3B).[13] As hemoglobin levels fell below normal, there was a linear increase in the incidence of de novo heart failure,[13] suggesting that moderate anemia was a potential risk factor for heart failure.

Intervention. Partial correction of severe anemia with erythropoietin-stimulating agents was associated with regression of hypertrophy in cohort studies (i.e., without a control group),[243] but in an RCT of full correction of anemia, compared to partial correction, changes in LV mass index and LV volume index were similar in both groups.[244] In addition, CV event rates were similar in diabetic CKD patients with moderate anemia treated with darbepoetin alpha compared to placebo.[227] This suggests that moderate anemia is not a cause of cardiac disease in CKD but a marker for some other unidentified cardiomyopathic factors associated with CKD.

The partial correction of severe anemia with erythropoietin-stimulating agents in dialysis patients has had a substantial impact on blood transfusion rates and has improved patients' quality of life,[245] although the safety of this intervention is unknown. Normalization of hemoglobin with erythropoiesis-stimulating agents was associated with harm, such as strokes,[227,244] vascular access clotting,[246] and hypertension.[247] It seems reasonable to prevent hemoglobin levels from falling below 9 g per deciliter using erythropoietin-stimulating agents to prevent transfusions and to maintain it in the 10 to 11.5 g per deciliter range to improve quality of life.

Hypoalbuminemia. Several studies have shown that hypoalbuminemia is a powerful predictor of poor outcome in the different groups of patients with CKD. It has been associated with CAD events in CKD (Table 79.1),[131] with de novo heart failure and ischemic heart disease events in dialysis patients (Table 79.3A),[189] and with de novo heart failure in renal transplant recipients (Table 79.3B).[13] The mechanisms underlying this association are unknown. Hypoalbuminemia may be a marker of a chronic inflammatory state, a hypercoagulable state, malnutrition, inadequate dialysis, or vitamin deficiency, all of which hypothetically could accelerate myocyte death and the development of cardiomyopathy, as discussed previously.

Inflammation

Predictor of cardiovascular events. Markers of inflammation have been associated with CV events in dialysis patients. CRP is an acute phase reactant, which is elevated in inflammation and is a predictor of CV death and of sudden cardiac death in incident dialysis patients.[248] In the 4D study of prevalent diabetic hemodialysis patients, CRP was strongly

associated with CV events and mortality, and was a much better predictor of these events than LDL cholesterol.[198]

Endotoxemia may be a cause of inflammation because CKD patients are exposed to endotoxemia from the gut, which is induced by systemic circulatory stress and recurrent regional ischemia. Endotoxemia is associated with systemic inflammation, malnutrition markers, cardiac injury, and reduced survival.[249] Soluble endotoxin receptor CD14 may result from subclinical endotoxemia, and was an independent predictor of mortality among prevalent patients on hemodialysis.[250]

Circulating plasma advanced glycation end products (AGE) accumulate in CKD. AGEs bind to their receptor for advanced glycation end products (RAGE) and induce an inflammatory response. Soluble RAGE (SRAGE) is shed from the cell-surface RAGE and binds circulating ligands, thus antagonizing downstream RAGE signaling. S100A12 is an extracellular newly identified RAGE binding protein (EN-RAGE), which is a ligand for RAGE. Circulating S100A12 and SRAGE are both elevated in hemodialysis patients. However, in prevalent patients, only S100A12 is associated with mortality, which is partly explained by its link with inflammation.[251]

Intervention. Statins may reduce inflammation in CKD. In the 4D study of 1,255 diabetic hemodialysis patients, CRP levels remained stable at 6 months on atorvastatin but increased in the placebo group.[197] Although CRP levels were highly predictive of outcome, atorvastatin treatment was not associated with reduced relative risks in the composite vascular end point or mortality. Aspirin may also reduce inflammation (see the following).

Hyperfibrinogenemia. Hyperfibrinogenemia is an independent predictor of CAD in CKD (Table 79.1).[131] Aspirin exerts its beneficial effect on the CV system by improving the procoagulant milieu that predisposes one to atherosclerotic events. In one large meta-analysis of non-CKD patients examining primary prevention of CAD, the absolute benefit of aspirin was a 0.15% reduction per year in MI compared with an increased risk of 0.04% per year for major noncerebral hemorrhage (noncerebral bleeds causing death, transfusion, or surgery) and 0.18% per year for minor hemorrhage.[252] Among hemodialysis patients (n = 2,632) in 14 RCTs, antiplatelet therapy resulted in a 41% reduction in CV events.[252]

Aspirin therapy probably worsens the platelet defects in CKD and increases the risk of bleeding. Despite these risks, patients with overt CVD should probably be prescribed low-dose aspirin to reduce the risk of subsequent CV events.[253] However, individual treatment decisions must be based on the considerations of patients' individual risks, likely benefits, and preferences.

Troponin levels. Troponin T and I are markers of myocardial injury. In ESRD patients not suspected of having acute coronary syndrome, elevated levels of troponin T (> 0.1 ng per milliliter) identified a subgroup who had poor survival and a high risk of cardiac death.[254] Troponin T may be a potential risk stratification tool, and the myocardial injury for which it is a marker may eventually be modifiable.

Oxidative Stress

Predictor of cardiovascular events. Oxidative stress occurs when there is an imbalance between the formation of reactive oxygen species (ROS) and antioxidant defense mechanisms. A number of enzymatic and nonenzymatic defense mechanisms have evolved to "detoxify" ROS. The predominant nonenzymatic agents include vitamin E, vitamin C, selenium, and zinc. Superoxide dismutase and glutathione peroxidase are the main antioxidant enzymes. Enhanced oxidative stress may be identified by an increase in the products of lipid peroxidation (e.g., malondialdehyde), a decrease in substances that enhance oxidative resistance (e.g., plasmalogen), or a decrease in reducing substances (e.g., glutathione). It is thought that oxidative stress is important in the formation of atheroma, but the ability of oxidative stress biomarkers to predict CVD has yet to be established.[255,256]

In CKD, markers of oxidative stress are increased. In fact, inflammation and oxidative stress are evident early in autosomal dominant polycystic kidney disease, even with normal renal function.[257] Dialysis may also further contribute to oxidative stress through the removal of antioxidants or through the stimulation of ROS by the use of incompatible dialysis components. However, the role of oxidative stress as a predictor of subsequent CV events has not been evaluated in large longitudinal studies.[258]

Two small RCTs in ESRD have reported good outcomes with antioxidants. In 196 hemodialysis patients, 800 U of vitamin E was compared to placebo in the secondary prevention of CVD, and a significantly lower incidence of ischemic events was reported.[259] In the other RCT, acetylcysteine (600 mg BID) was compared to placebo in 134 hemodialysis patients and also reported a significantly lower incidence of composite ischemic events.[260]

However, the Heart Outcomes Prevention Evaluation (HOPE) study[261] found no significant difference in the composite primary outcomes (MI, stroke, or CV death) using vitamin E in patients with moderate CKD (serum creatinine, 1.4 to 2.3 mg per deciliter). Furthermore, in HOPE – TOO,[262] where 3,994 enrolled patients continued to take study medication (ramipril, vitamin E, or placebo), there were no differences in CV events with vitamin E therapy on longer follow-up, but there were higher rates of heart failure. These dissonant results do not permit recommendations in favor of antioxidant therapy at present.

Homocysteine

Predictor of cardiovascular events. Homocysteine is a by-product of methionine metabolism, a sulfhydryl-containing essential amino acid, and lies at the junction of two metabolic pathways, transsulfuration and remethylation. The rate of homocysteine elimination is facilitated by cofactors,

particularly B_{12} and folate. Progressive renal failure is associated with increasing homocysteine levels: 83% of patients have levels above the 90th percentile for the general population by the time they reach ESRD,[263] and prospective studies suggest an association between homocysteine and combined CV end points in hemodialysis patients and renal transplant recipients.[264,265]

Intervention. High-dose folate supplementation (15 mg per day) can reduce but does not normalize homocysteine levels in ESRD.[266] An improvement in clinical outcomes for dialysis patients with high-dose folic acid relative to low-dose supplementation (i.e., 1 mg per day) was not observed.[267] In CKD patients and in renal transplant recipients, therapy with supraphysiologic doses of vitamins B_6, B_{12}, and folic acid may reduce homocysteine to normal levels.[266] However, a RCT of vitamin B therapy versus placebo in 283 patients with diabetic nephropathy demonstrated that, rather than lowering vascular events, the intervention was associated with an increase in these events and a greater decrease in GFR.[268]

In an RCT of 650 hemodialysis patients randomized to a high dose of combined B vitamins and compared to a low-dose total mortality did not differ between the two arms of the study, but there was a nonsignificant 20% reduction in the risk of CV events in the high-dose arm (HR, 0.8; 95% CI, 0.60 to 1.07).[269]

A definitive answer may be likely when the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial is completed.[270] This study has enrolled 4,110 renal transplant recipients to assess the impact of high doses of folic acid, B_6, and B_{12} on CV events.

Increased extracellular volume. Salt and water overload is a persistent problem in patients on dialysis and is also problematic in patients with CKD and in renal transplant recipients. LV diameter changes with changes in blood volume in hemodialysis patients.[271] Observational studies suggest that greater interdialytic weight gain and noncompliance with the prescribed dialysis regimen are independently associated with higher blood pressure.[272,273] In a prospective study of peritoneal dialysis patients, sodium and fluid removal as well as hypertension were predictive of death within 3 years of starting dialysis.[273] LVH is possibly more severe in long-term peritoneal dialysis patients, a finding that is associated with pronounced volume expansion, hypertension, and hypoalbuminemia.[274]

High natriuretic peptide levels can result from volume expansion and/or myocardial dysfunction. Levels of B-type natriuretic peptide (BNP) are highest in patients who are on dialysis and have CV comorbidities.[275] In patients with CKD, serum BNP can be elevated and high BNP levels are a predictor of progressive renal disease and mortality.[276,277] In incident hemodialysis, patients' N-terminal pro-BNP (NT pro-BNP) was an independent predictor of future CV events.[19]

In the 4D study of prevalent diabetic hemodialysis patients, high baseline and increasing levels over time in N-terminal pro-BNP were predictive for sudden cardiac death, CV events, and mortality.[201] In 965 peritoneal dialysis patients enrolled in a trial[278] of increased quantity of dialysis using peritoneal dialysis, baseline values of natriuretic peptides were elevated and were inversely correlated with levels of residual renal function. The relative risk of NT pro-BNP for the bottom two quintiles compared to the remainder was 0.63, which was significant and independent of multiple other predictors. Whether the high BNP levels were associated with increased blood volume, and thus potentially modifiable by interventions to normalize blood volume, is unknown, but this seems likely. Trials to assess the clinical impact of interventions that maintain normal blood volume should be undertaken.

Arteriovenous Fistulae

Blood flow in arteriovenous fistulae and grafts predisposes a patient to LV volume overload. In one study, 20 renal transplant recipients with a mean fistula flow of 1790 ± 648 mL per minute were assessed.[279] Three to 4 months after fistula closure, LV end-diastolic diameter decreased from 51.5 to 49.3 minutes ($P < .01$) and the LV mass index fell from 135 to 120 g per square meter ($P < .01$). These findings were confirmed in another similar study.[280]

Abnormalities in Divalent Ion Metabolism

Predictor of cardiovascular events. An attractive hypothesis that is gaining traction is that disturbed divalent ion metabolism promotes vascular calcification, which produces noncompliant large conduit vessels. This in turn predisposes the patient to LVH, cardiac failure, and subsequent death.

Hyperphosphatemia usually develops as kidney function deteriorates and is a common problem among patients with ESRD. Phosphate combines with calcium in the blood and the resultant hypocalcemia induces secondary hyperparathyroidism. The persistent overstimulation of the parathyroid glands engenders autonomous growth, and this tertiary hyperparathyroidism may be associated with hyperphosphatemia, increased calcium X phosphate product, and elevated parathyroid hormone (PTH) levels.

In a study of 12,833 patients undergoing hemodialysis,[281] a 0.3 mmol per liter incremental increase in serum PO_4 levels was associated with a 9% increase in the risk of death related to CAD and a 6% increase in the risk of sudden cardiac death. Deaths related to CAD and sudden cardiac death correlated with elevated levels of Ca × PO_4 product in a linear manner. Sudden cardiac deaths were also related to log parathyroid hormone in a nonlinear fashion (U-shaped relationship), but were strongly associated with serum parathyroid hormone > 52.1 ng per liter (RR, 1.25; $P < .05$).[281] An analysis of 40,538 prevalent hemodialysis patients from the U.S. Renal Data System (USRDS) registry also demonstrated that high serum phosphate, serum calcium, and

serum parathyroid hormone concentrations were associated with increased all-cause and CV mortality.[282] These two studies included only survivors of dialysis, thus limiting the conclusions that can be made. The CHOICE study[194] enrolled incident hemodialysis patients, and confirmed the adverse impact of divalent ion abnormalities. This prospective study of 776 hemodialysis and 259 peritoneal dialysis patients had a median follow-up of 2.5 years, during which time 460 deaths occurred. The adjusted RR of death for time-dependent serum phosphate levels > 6.0 mg per deciliter was 1.6 (95% CI, 1.1 to 2.3); for time-dependent serum calcium levels > 9.7 mg per deciliter, it was 1.5 (95% CI, 1.0 to 2.3); and for time-dependent PTH levels > 308 pg per milliliter, it was 1.7 (95% CI, 1.0 to 2.8). The association between high PTH levels and mortality was confirmed in the 4D study, but this impact was nullified in those who had wasting, which was defined by serum albumin levels < 3.8 g per deciliter and a BMI < 23.[199]

The adverse outcomes associated with hyperphosphatemia in dialysis patients have been extended to patients with predialysis CKD and to community-based cohorts. In patients with CKD, data from the Veterans' Affairs Consumer Health Information and Performance Sets (CHIPS) of 6,730 patients with CKD revealed that a serum phosphate level > 3.5 mg per deciliter was associated with mortality independent of other risk factors and eGFR.[283] In 1,036 stage 3 and 4 CKD patients from a single United Kingdom center, the highest quartile of serum phosphate compared to that in the lowest quartile was a predictor of all-cause and CV mortality, independent of age, gender, proteinuria, eGFR, diabetes, hemoglobin (Hb), systolic BP, current smoking, CVD, renal replacement therapy, vitamin D analog use, and phosphate binder use.[284] However, it is possible that serum phosphate colocalizes with some other factor(s) associated with CKD that actually causes CVD.

Five community-based prospective cohort studies examined the relationship between serum phosphate and CVD. Graded associations with cardiac calcification, LVH, CV events were observed, and CV risk seemed to accelerate with serum phosphate 3.5 to 4 mg per deciliter.[285]

In CKD, fibroblast growth factor 23 levels are increased to maintain normal concentrations of serum phosphate. Increased levels are associated with increased LV mass and an increased risk of LVH in predialysis CKD patients.[286]

In 1,094 participants in the African American Study of Kidney Disease Hypertension (AASK), following an adjustment for demographics, drug and BP groups, comorbidity, liver function, serum calcium, and phosphorus, each doubling of serum alkaline phosphatase was associated with a HR of 1.55 (95% CI, 1.03 to 2.33).[287] It is possible that raised serum alkaline phosphatase reflects more severe hyperparathyroidism or vitamin D deficiency.

Levels of 25-hydroxyvitamin D were measured in 1,108 diabetic hemodialysis patients in the 4D study and followed for a median time of 4 years.[200] Severe vitamin D deficiency was strongly associated with higher rate of sudden cardiac death and CV results. However, whether vitamin D supplementation will decrease these adverse outcomes is unknown.

Evidence to support the link between divalent on abnormalities and metastatic calcification has also evolved. An increased prevalence and the extent of coronary artery calcification, particularly in young dialysis patients, has been significantly associated with higher serum phosphate, calcium–phosphate product, and calcium intake.[17] Whether this calcification represents specific changes within atherosclerotic plaques or is a stage associated with arteriosclerosis is not clear. The presence of vascular calcification in hemodialysis patients was associated in one study with increased stiffness of large capacity, elastic-type arteries such as the aorta and the common carotid artery. The extent of arterial calcifications increased with the use of calcium-based phosphate binders.[17] As discussed earlier, aortic calcification is predictive of death in dialysis patients.[184]

Treatment. Patients with CKD are in substantial positive calcium balance from an early stage of the disease. Attempts to minimize the calcium X phosphate product by treating hyperparathyroidism and by phosphate control have a sound teleologic base, as does the appropriate use of vitamin D analogs. However, evidence of better CV event outcomes with these therapies compared to placebo have not been reported. The relative benefits of sevelamer hydrochloride (a noncalcium, noncarbonate binder) was compared to calcium carbonate in 114 hemodialysis patients. It showed that at 52 weeks, patients treated with calcium carbonate had significant increases in coronary artery (34%, P < .01) and aortic (32%, P < .01) calcification compared to the sevelamer-treated patients.[111]

Cinacalcet is a calcimimetic, which reduces parathyroid hormone levels. In 360 hemodialysis patients with moderate-to-severe secondary hyperparathyroidism, an RCT of cinacalcet plus low-dose vitamin D sterols compared to flexible doses of vitamin D sterols alone was recently reported.[112] Increases in calcification scores were consistently less in the aorta, in the aortic valve, and in the mitral valve among the cinacalcet group and the differences were significant at the aortic valve. Whether these observations translate into improvement in CV outcomes is unknown.

An observational study of 19,186 hemodialysis patients, 5,976 of whom received cinacalcet, reported a significant lower all-cause mortality among cinacalcet-treated patients compared with nontreated patients (adjusted HR, 0.74; 95% CI, 0.67 to 0.83).[288] Like all observational studies, adjustment for multiple different potential confounding factors does not remove the bias caused by selecting particular patients for cinacalcet therapy. Consequently, one should await the results of the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study before adopting cinacalcet as a strategy to reduce CV events in patients with secondary hyperparathyroidism. This is an RCT that has enrolled around 4,000 hemodialysis patients comparing cinacalcet to placebo, and has as its primary end point a composite of major CV events.[289]

Iron Overload

The role of iron in the pathogenesis of CVD in patients with ESRD is not well defined; iron overload has, however, been associated with elevated rates of hospitalization and mortality in patients with ESRD.[290] Iron can promote the production of ROS and free radicals resulting in intercardiomyocytic fibrosis. In a study of 102 nondiabetic patients undergoing peritoneal dialysis who were matched with 102 healthy patients with a serum creatinine level < 133 μmol per liter (1.5 mg per deciliter), the mean QTc dispersion among the patients was significantly longer than in control participants (69.8 ± 40.0 versus 55.2 ± 33.6 ms; P < .01).[291] High iron saturation > 35.2% was an independent factor for QTc dispersion longer than 74 ms (sensitivity, 71.4%; specificity, 55.3%; r = 0.432; P < .001).

Sympathetic Overactivity

Sympathetic overactivity is an early event in the pathophysiology of acute and chronic kidney injury of various etiologies. Augmented sympathetic drive is seen even during hemodialysis sessions, suggesting that this event is volume independent. Such events usually subside following a bilateral nephrectomy.[292] Sympathetic overactivity may aggravate hypertension, ventricular hypertrophy, and heart failure and may result in an increased risk of sudden cardiac death.[52]

Autonomic imbalance may result from high sympathetic tone and/or low parasympathetic tone, and can be assessed using heart rate variability measurements. In the ARIC study, a higher resting heart rate and lower heart rate variability were significantly associated with incident ESRD and CKD-related hospitalizations.[293]

In 239 subjects enrolled in the Frequent Hemodialysis Network Trial Holter monitor findings were characterized by sympathetic overactivity and vagal withdrawal, and were associated with a higher LV mass.[56] As discussed earlier, β-blockers, which diminish sympathetic activity, have been shown to improve some CV outcomes in CKD.

Obstructive Sleep Apnea

Obstructive sleep apnea causes episodes of nocturnal arterial oxygen desaturation, and this syndrome occurs more frequently in patients undergoing dialysis compared with the general population. In 30 clinically stable hemodialysis patients, 25 (83%) had sleep disordered breathing, with an apnea–hypopnea index > 5 episodes per hour. The percent of sleeping time with saturated arterial 0_2 < 90% was 4.2%.[294] In the 4D study, 40% of people who died as a result of sudden cardiac arrest were found dead in bed in the morning.[145] The investigators postulated that this outcome might be related to obstructive sleep apnea. This suggestion was supported by a recent study. Of 93 prevalent peritoneal dialysis patients, 51 were diagnosed with sleep apnea syndrome, which was a predictor of mortality independent of age, gender, and diabetes.[295] The absolute increase in the apnea–hypopnea index was associated with incremental risk of CV events. In addition, nocturnal hypoxemia and night–day arterial pressure changes have been linked to LV geometry in dialysis patients.[55] Sleep apnea is improved by daily dialysis[56] but whether this translates into better CV outcomes is unknown.

Mode of Dialysis Therapy

Although RCTs in hemodialysis patients[296] and in peritoneal dialysis patients[297] failed to show that an increased quantity of dialysis improved clinical outcomes, suggestive evidence has recently been reported that nocturnal/daily dialysis may have a beneficial effect on the heart. Culleton et al.[298] have demonstrated an improvement in LV mass index measured by magnetic resonance imaging (MRI) in those randomly allocated to daily hemodialysis compared to conventional dialysis. In the Frequent Hemodialysis Network Trial, 125 patients were randomly allocated to hemodialysis six times per week and were compared to 120 patients allocated three times per week.[121] Frequent hemodialysis was associated with a significant benefit for the coprimary outcome, death or increase in LV mass measured using MRI (HR, 0.61; 95% CI, 0.46 to 0.82); improved control of hypertension; and improved control of hyperphosphatemia. It is possible that these beneficial effects on the cardiac structure are mediated by better blood volume control, and daily dialysis certainly has the potential to prevent CV events.

A cohort study of 94 patients who were treated with nocturnal hemodialysis was compared to 10 propensity score–matched controls treated with conventional hemodialysis for each patient.[299] Nocturnal hemodialysis was associated with significant reductions in mortality risk (HR, 0.36; 95% CI, 0.22 to 0.61) and in risk for death, acute MI, or stroke (HR, 0.56; 95% CI, 0.35 to 0.89).

It has been postulated that more atherogenic lipid profiles in peritoneal dialysis patients could predispose them to more atherosclerotic events and that the intermittent blood volume increases seen in hemodialysis patients could predispose them to more heart failure events. Evidence to support the former hypothesis was reported from outcomes in 24,587 patients who commenced dialysis in Australia and New Zealand between 1997 and 2008.[300] Peritoneal dialysis was consistently associated with an increased hazard of CV death compared to hemodialysis after 1 year of treatment. This increased risk in peritoneal patients was largely associated with an increased risk of death due to MIs. Surprisingly, in an analysis of registry data from more than 100,000 incident dialysis patients, patients with CHF treated with peritoneal dialysis had higher levels of mortality over 2 years compared to hemodialysis patients (RR, 1.24; 95% CI, 1.14 to 1.35).[301]

Multiple Risk Factor Intervention

The objective of enhancing the appropriate use of interventions to slow the progression of renal disease and to prevent CVD requires a multifaceted, multidisciplinary approach,

which may not be feasible with current primary care–provided models. Furthermore, the poor outcomes of CVD in ESRD suggest that a preventive strategy at an earlier phase of CKD may be more fruitful than a secondary prevention strategy after cardiac events have occurred. This strategy would require risk intervention in multiple factors simultaneously. The excellent results achieved in an RCT[302] of diabetic patients receiving intensive therapy, and of heart failure patients treated in multidisciplinary clinics, suggest that a similar approach in patients with CKD could produce better outcomes than conventional health care delivery models.

Recently, a RCT of 474 stage 3/4 CKD patients identified in the community was reported examining a nurse-coordinated model of care for multiple risk factor interventions versus usual care determined by the family doctor.[303] The important conclusions were (1) patients with CKD identified through community laboratories largely had nonprogressive kidney disease but had quite a high rate of cardiovascular events, (2) the nurse-coordinated model during the 2-year study provided similar control of most risk factors compared to conventional management and was associated with more use of appropriate drugs in eligible patients, and (3) it was less costly.[303,304] Whether this model of care can improve renal and CV outcomes in patients with progressive kidney disease requires investigation.

Interventions for Symptomatic Cardiac Disease

Ischemic Heart Disease

There are no randomized trials concerning the treatment of either the acute coronary syndrome (unstable angina and acute MI) or the nonacute presentations of CAD (stable angina and CHF) in patients with CKD. In the absence of such data, the treatment should be the same as in the nonuremic population. Unfortunately, observational data suggest that dialysis patients with an acute MI are far less likely to receive standard therapy (i.e., aspirin, β-blockers, and ACE inhibitors) compared to other patients.[305] Control of extracellular fluid volume and partial correction of severe anemia with erythropoietin-stimulating agents is a therapeutic adjunct specific to CKD patients, particularly those on dialysis.

Medical Management

As in the general population, patients with CKD and stable angina pectoris who have not had an MI should be treated with antianginal agents for the relief of symptoms. Coronary arteriography is recommended for patients with symptoms at rest or after minimal exertion, LV dysfunction, or signs of severe ischemia at low level of exercise during a stress test. For patients who have had an MI, β-adrenergic blockers are recommended indefinitely, as is an ACE inhibitor for patients with LV dysfunction.[306] In the general population, aspirin therapy is of proven benefit in the treatment of acute MI and after acute MI, as well as for long-term use in patients with a wide range of prior manifestations of CVD.[307] Although far fewer data are available for the CKD population, a study of 1,724 patients with an acute MI categorized patients into quartiles based on their renal function. In the group with the lower GFR (< 46.3 mL per minute), aspirin and β-blocker use was the lowest among all groups of patients, yet the observed risk reduction was similar among all ranges of GFR. This suggests that aspirin and β-blockers are at least as effective in CKD and in dialysis patients as in the nonrenal-failure populations.[308] This, combined with the substantial improvement in CVD outcomes in nonuremic patients with preexisting CVD, is sufficient to recommend that patients with CKD or ESRD with ACS or established CAD should be treated with aspirin and β-blockers in a manner similar to patients with normal renal function.

Although the general population appears to benefit from newer antiplatelet therapies such as aspirin plus clopidogrel,[309,310] the relative safety and efficacy of such a treatment in patients with CKD or ESRD is not yet known.

There is overwhelming evidence that the treatment of dyslipidemia in the general population for the secondary prevention of atherosclerotic events provides substantial survival benefit. In view of the data presented earlier, it seems reasonable to treat CKD patients in a similar manner, provided that life expectancy is such as to benefit from these drugs.

Revascularization

Coronary artery bypass graft surgery. The potential risks and benefits of coronary revascularization procedures in patients with CKD or ESRD are different from those in the general population. The reported perioperative mortality rate of CABG surgery in patients on dialysis has ranged from 0% to 20%, which is significantly higher than in the general population, but the studies on which these figures are based are mostly small and retrospective, and do not make adjustment for comorbid factors. When the results of these studies are combined, the perioperative mortality rate is approximately 8% to 9%, roughly three times the expected rate for patients without ESRD.[311–313] The perioperative morbidity rate of CABG surgery is also greater, both in patients on dialysis and nondialysis-dependent patients with CKD than in matched control patients.[314–316] The 5-year cumulative survival rate of patients on dialysis after CABG is approximately 50%.[311,312] These survival rates are comparable with those seen in the overall ESRD population, but are considerably lower then the overall 5-year survival rate of 85% after CABG, as observed in the Coronary Artery Surgery Study.[317] There are few data as to the outcome of revascularization procedures in patients who have had renal transplantation. Transplanted patients with near normal renal function have a perioperative mortality rate and long-term survival rate close to those observed in the non-ESRD population.[318,319]

The only randomized trial of revascularization versus medical therapy in patients with ESRD to date enrolled 26 asymptomatic diabetic patients who were found to have CAD on screening coronary angiography before renal transplantation.[320] Ten of 13 medically managed and 2 of

13 revascularized patients had a CV end point (unstable angina, MI, or cardiac death), and the trial was stopped early by an external review committee. This provides some evidence that revascularization may improve the prognosis of asymptomatic CAD in this select population, but medical therapy in this instance consisted only of a calcium channel–blocking drug and aspirin. Regardless of any survival benefit, CABG usually offers good relief from angina.[314]

Coronary artery stenting. The role of percutaneous transluminal angioplasty (PTCA) in the CKD or ESRD patients is controversial. Despite a high rate of initial technical success in patients with ESRD, PTCA seems to be associated with frequent recurrence of symptoms, usually resulting from restenosis.[312,321,322] PTCA with stenting of dilated vessels in the dialysis population is certainly feasible, but patients treated with PTCA compared to CABG do have a significantly higher long-term risk of MI or a recurrence of ischemic symptoms.[311] CABG appears to have better outcomes in dialysis patients than PTCA with or without stenting.[323,324] However, it is important to remember that all comparisons between vascularization procedures in CKD patients are from registries or observational studies, and thus are prone to selection bias and confounding by indication. Herzog et al.[324] analyzed USRDS data from dialysis patients undergoing their first revascularization procedure. After comorbidity adjustment, the RR for CABG (versus PTCA) patients was 0.80 (95% CI, 0.76 to 0.84), for all-cause death, and 0.72 (95% CI, 0.67 to 0.77) for cardiac death. For stent (versus PTCA) patients, the RR was 0.94 (95% CI, 0.88 to 0.99) for all-cause death, and 0.92 (95% CI, 0.85 to 0.99) for cardiac death.[324] To date, there have been no studies comparing PTCA with medical management of patients with ESRD or CKD and CAD.

The recent advent of drug-eluting stents may be a step forward in the management of CAD. In a large registry of all comers for percutaneous coronary intervention, CKD was an independent predictor of adverse late outcomes.[325] In patients with ESRD requiring hemodialysis frequencies of restenosis and 2-year major adverse cardiac event rates after sirolimus-eluting stent implantation were markedly higher than in nonhemodialysis CKD patients.[326] However, the selective use of drug-eluting stents in patients with CKD was safe and effective in the long term, with a lower risk of all-cause death, target vessel revascularization, and major adverse cardiac events, and a similar risk of MI and stent thrombosis as compared with bare metal stents.[327] In another registry study,[328] the results in patients with severely decreased GFR were not as impressive. In patients with nondialysis CKD and multivessel CAD, CABG was associated with better survival than angioplasty and placement of drug-eluting stents, but CABG patients had a greater short-term risk of requiring permanent hemodialysis.[329]

In summary, the indications for coronary revascularization in patients with CKD or ESRD are, in general, the same as those in the nonuremic population. Revascularization appears to be beneficial in high-risk patients. Those with persistent symptoms of myocardial ischemia, despite maximal medical therapy, should have a coronary arteriography to identify critical coronary stenosis, provided that their life expectancy is otherwise reasonable. Based on the existing evidence, CABG appears to be the revascularization procedure of choice. PTCA with a drug-eluting stent seems to be a reasonable alternative in single-vessel disease or multiple-vessel disease with culprit lesions.

Congestive Heart Failure

For all patients with symptoms of heart failure, potentially reversible precipitating and aggravating factors (e.g., ischemia, tachycardia, dysrhythmias, or hypertension) should be sought and appropriately managed. The treatment of heart failure differs for those with systolic and diastolic dysfunction in that inotropic agents such as digoxin and vasodilators should be avoided in those with diastolic dysfunction.

β-Adrenergic receptor blockers. A large amount of data from recent, well-designed trials supports the use of β-adrenergic receptor antagonists in the management of LV systolic dysfunction. Improvement in mortality or hospitalization rates have been shown in patients with mild-to-moderate symptomatic heart failure treated with carvedilol, bisoprolol, or controlled-release metoprolol.[330] The use of β-receptor antagonists with intrinsic sympathomimetic activity appears to be detrimental, and these agents should not be used in patients with heart failure. Current guidelines for the general population suggest the routine use of β-receptor antagonists in clinically stable patients with an LV ejection fraction $<$ 40% and mild-to-moderate heart failure symptoms who are on standard therapy (e.g., diuretics, ACE inhibitors, and digoxin).[330] Such therapy also should be considered for asymptomatic patients with an LV ejection fraction $<$ 40%, but the evidence supporting its use in this setting is not as strong. In one of the few randomized trials performed in dialysis patients, Cice et al.[331] have demonstrated that carvedilol treatment in patients with dilated cardiomyopathy reduced 2-year mortality (51.7% in the carvedilol group, compared with 73.2% in the placebo group [$P < .01$]). There were fewer cardiovascular deaths (29.3%) and hospital admissions (34.5%) among patients receiving carvedilol than among those receiving a placebo (67.9% and 58.9%, respectively; $P < .00001$). This supports the notion that β-receptor antagonists may be safely used in the CKD and ESRD population in the same manner recommended for the general heart failure population. As in the nonrenal-failure population, however, the agents should be started in low doses with careful clinical reevaluations during the titration phase.

Angiotensin-converting enzyme inhibitors/blockers. The use of this class of drugs for the management of heart failure has been well demonstrated in the general population. ACE inhibitors have been found to improve symptoms,

reduce morbidity, and improve survival, thus making them an important component of CHF therapy.[330] Although trials in the CKD or ESRD population have not been conducted, the high degree of benefit shown in other patients makes it very reasonable to treat these patients in a similar manner. Therefore, ACE inhibitor therapy is recommended for patients with symptomatic heart failure, for post-MI patients with an LV ejection fraction < 40%, and for asymptomatic patients with an LV ejection fraction less than 35%.[330] Angiotensin II–receptor blockers are good alternatives to ACE inhibitors in the treatment of heart failure for those who cannot tolerate ACE inhibitors.

In the absence of large, double-blinded randomized controlled trials in patients undergoing dialysis, the use of ACE inhibitors, ARBs, or both should follow indications derived from trials in patients without renal disease.

Digoxin. In the nonrenal population, digoxin may be beneficial in the treatment of heart failure and atrial fibrillation. However, in hemodialysis patients, digoxin use has been associated with excess mortality.[332] It should be noted that the research design in the study was observational and thus limited by selection bias. However, digoxin levels > 1.0 ng per milliliter were associated with excess mortality, which is consistent with the belief that the narrow therapeutic window, the long half-life, and the potential for lethal arrhythmias, especially in the presence of hypokalemia, make digoxin a poor choice for use in ESRD patients.

Diuretics. These drugs remain an essential component of the symptomatic treatment for heart failure in nondialysis-dependent patients with CKD, although multiple agents at high doses may be required in patients with more advanced renal impairment. Loop diuretics are widely used to maintain euvolemia in most patients with CHF, but their effect may be negligible in patients requiring dialysis. Thiazide diuretics usually become ineffective with a GFR < 30 mL per minute and are therefore not useful in patients with severe renal impairment. Aldosterone antagonists are similarly ineffective in patients with ESRD, but hyperkalemia can result when these drugs are combined with renin angiotensin system blockade and β-receptor antagonists. They should be avoided in such patients.

Warfarin in atrial fibrillation. An observational study (DOPPS)[141] identified an increased risk of stroke associated with warfarin use in dialysis patients with atrial fibrillation, a risk also identified in another study.[333] For patients with CKD, atrial fibrillation and a CHADS2 score ≥ 2 anticoagulation with warfarin has been recommended, provided there is access to high quality monitoring of coagulation.[334]

Cardiac Arrest

Automated external defibrillators. A total of 110 cardiac arrests in two hemodialysis facilities in King County, Seattle, Washington, were identified over 14 years; 65% of these events occurred during hemodialysis sessions and were secondary to ventricular fibrillation.[35] The risk of ventricular fibrillation was much higher after the dialysis session compared with the period during dialysis. Thirty-four cardiac arrests occurred after an automated external defibrillator was made available within the dialysis units. However, these devices were only used in 50% of these arrests. A shock was delivered on 83% of the occasions when the defibrillator was used. Survival to hospital discharge was not notably different between patients who arrested before or after an external defibrillator was provided at the dialysis unit.[335] Although data do not exist to support a survival benefit of external defibrillator placement in dialysis centers, it seems reasonable to provide them for use in patients who want resuscitation if they arrest.

Implantable cardioverter-defibrillators. Implantable cardioverter-defibrillators (ICDs) decrease the risk of sudden cardiac death, but the majority of trials using these devices have excluded patients with advanced renal insufficiency. Dasgupta et al.[336] reported complication rates for cardiac rhythm management devices (permanent pacemakers or ICDs) in 41 patients with ESRD and in 123 control participants without ESRD. Major complications (such as pneumothorax requiring a chest tube, a pocket infection requiring device extraction, or thrombosis) occurred in 29% of ESRD patients versus 5% of controls (P < .03). No fatal complications occurred in either group. Furthermore, patients with advanced renal insufficiency could be less responsive to ICD therapy, probably owing to higher defibrillation thresholds.

In a retrospective study[337] of 230 patients who received an ICD for primary or secondary indications, renal insufficiency was a strong predictor of an arrhythmia eliciting appropriate ICD shocks. Patients with higher degrees of renal dysfunction were more likely to have shorter times to ICD therapy (defined as shock and antitachycardia pacing). Patients were divided into three groups according to their serum creatinine levels (< 88.4 μmol per liter, 88.4 to 123.8 μmol per liter, and > 123.8 μmol per liter). The 1-year incidence of appropriate ICD shock was 3.8%, 10.8%, and 22.7% in these groups, respectively (P = .003). The 1-year incidence of any appropriate ICD therapy was 8.8%, 20.8%, and 26.3% (P = .02). Serum creatinine was an independent predictor of the time to first appropriate ICD shock (HR, 6.0 for the third group compared with the first group; P = .001) or the first appropriate ICD therapy (HR, 3.0 for the third compared with the first group; P = .015). Seven patients (3%) were on hemodialysis at the time of device implantation. These patients experienced more appropriate ICD shocks for documented ventricular tachyarrhythmias than those not undergoing dialysis (57% versus 11%; P = .006). The 1-year incidence of appropriate ICD shock was 37.5% for patients on dialysis and 10.7% for those not on dialysis (P < .0001), and the 1-year incidence of any appropriate ICD therapy for patients on dialysis versus those not on dialysis was 33.3% versus 16.5% (P = .0005).

Patients who received an ICD for the primary prevention of sudden cardiac death (n = 222) were stratified by CKD, defined as serum creatinine levels ≥ 176.8 μmol per liter, or on dialysis.[338] The 1-year survival for patients with (n = 35) and without (n = 194) CKD was 61.2% and 96.3%, respectively. CKD was the most significant independent predictor of mortality (HR, 10.5; 95% CI, 4.8 to 23.1). Furthermore, each 10 mL per minute drop in creatinine clearance was associated with a 55% rise in the HR of death ($P < .001$). It was concluded that in patients receiving an ICD for the primary prevention of sudden cardiac death, CKD significantly reduced long-term survival, which may limit the impact of ICD therapy in this patient population.

A decision analysis and Markov modeling of whether to implant a cardioverter-defibrillator for the primary prevention of sudden cardiac death in patients with CKD[339] found that the benefit of ICD use depends primarily on the patient's age and secondarily on the stage of kidney disease. ICDs reduce mortality in patients with stage 1 and 2 CKD, whereas the benefit is less notable in patients with stage 3 through 5 CKD, and the effect is age dependent. These findings could be attributed to a higher procedural risk and complications in addition to decreased life expectancy in patients with advanced CKD compared with control individuals.[340] With a standard procedural mortality of 0.5% per procedure, cardioverter-defibrillator implantation is preferential in patients < 80 years of age for stage 3 CKD (GFR, 30 to 59 mL/min/1.73 m^2), in patients < 75 years of age for stage 4 CKD (GFR, 15 to 29 mL/min/1.73 m^2), and in patients < 65 years of age for stage 5 CKD (GFR < 15 mL/min/1.73 m^2).[339] Thus, advanced stages of CKD and older age favor the no ICD strategy. No health technology assessment of ICD use in patients with CKD is available. However, a study published in 2005 showed that prophylactic ICD use in patients with heart failure has a cost-effectiveness ratio below US$100,000 per quality-adjusted life year gained, provided that the ICD reduced mortality by 7 years or more.[340]

CONCLUSIONS

CKD is a state of high cardiomyopathic, atherosclerotic, and arteriosclerotic disease. The high prevalence of traditional CV risk factors is partly responsible, including the modifiable factors of hypertension, smoking, hyperlipidemia, hyperglycemia, and obesity. Furthermore, uremia-related predictors of CV disease have been identified, including inflammation, hyperfibrinogenemia, high troponin levels, hyperhomocysteinemia, hypophosphatemia, hyperparathyroidism, and blood volume expansion caused by severe anemia, atrioventricular fistula/graft, and salt and water retention. Whether modification of these predictors will result in fewer CV events is unknown. Although the outcomes of the CV events in stage 4/5 CKD are worse than those in the general population, efficacious therapies are available. The greatest opportunity for improvement in CV outcomes lies in the prevention of CVD in the earlier phases of CKD, and in the development of interventions to modify uremia-related CV risk factors, particularly reducing inflammation, treating divalent ion abnormalities, and normalizing blood volume.

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