Atherosclerosis in elderly patients with renal insufficiency

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Introduction

As people age, cardiovascular structure and function change and this is superimposed on by specific pathophysiologic disease mechanism. In addition to lipid levels, diabetes, sedentary lifestyle, and genetic factors that are known risks for coronary disease, hypertension, and stroke - the quintessential cardiovascular (CV) diseases related to atherosclerosis within our society - advancing age unequivocally confers the major risk. (Fig. 1) Mortality due to cardiovascular disease is more than any other disease and creates enormous costs for the health care system. The main underlying problem in cardiovascular disease is atherosclerosis, a process that obstructs major arteries with lipid deposits and cell accumulation. Decreased kidney function (estimated GFR < 70 mL/min/1.73 m²) is an independent risk factor for cardiovascular disease and all-cause mortality in the general population.

In 2020 (35, 40, and 54 million individuals). The prevalence of moderately or severely decreased kidney function in this age group is 20.6% (SE, 1.1%) and is substantial even in the absence of diabetes or hypertension (10.8%; SE, 1.0%). Data from the NHANES III, a study of community-dwelling adults, estimated that 25% of all Americans 70 years of age and older had moderately or severely decreased kidney function.² Fig. 2. Physiological implications of many older individuals having less than half the kidney function of young adults are still unknown but are important to determine, given the aging of the population. Dosage adjustment of drugs excreted by the kidney; greater risk for such complications of CKD as anemia, bone disease, and malnutrition; and increased risk for developing kidney failure all need to be considered in the routine care of older individuals with a decreased GFR.

Fig. 2. Prevalence of decreased kidney function (GFR < 60 mL/min/1.73 m²) in the overall noninstitutionalized US population, as well as by history of diabetes and presence of hypertension: NHANES III, 1988 to 1994. (Reproduced with permission from Coresh, J., et al., Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41: 1-12.)

Epidemiology

Thirteen percent of the U.S. population is currently 65 years or older, and about half of these 25 million people have cardiovascular disease. By the year 2030, 1 in 5 Americans will be older than 65 years, with the subset older than 85 years increasing most prominently in size (Fig. 3)

Cardiovascular disease increases dramatically with aging and is the major cause of mortality and disability in elderly persons; 83% of all cardiovascular deaths in the United States occur in patients older than 65 years of age. Cardiovascular disease is also a major contributor to the need for hospital,
ambulatory, and custodial care. In 1987, two-thirds of the U. S. health care expenditures for cardiac disease (totaling $22.3 billion) was for patients older than age 65. Elderly patients are intensive users of emergency medical services and of medical services in general. Coronary heart disease is the most prevalent cardiac problem, followed by hypertensive cardiovascular disease, with valvular and pulmonary heart disease other important etiologies (Fig. 4-6). Despite these statistics, data is limited regarding cardiovascular disease in the octogenarian and beyond, compromising optimal clinical care for such patients. Cardiovascular disease at elderly age is additionally complicated by its frequent association with multiple other comorbid illnesses.

Currently, there are approximately 406,081 patients with end-stage renal disease (ESRD) in the United States. This hardly describes the impact of renal disease, because moderate chronic kidney disease (CKD), which is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73m², is nearly 10 times more prevalent than ESRD. The annual mortality rate for patients with ESRD is approximately 20%, and around fifty percent of these deaths are attributable to cardiovascular disease. Cardiovascular events are as much as 50 times more likely to occur in patients with ESRD than in the general population. In children with ESRD, cardiac death is 100 times more likely than in the general population and accounts for 23% of the mortality rate. Patients with CKD undergoing coronary revascularization also have an increased mortality rates. Greater degrees of renal dysfunction are associated with a higher mortality rate (risk ratio of death for a creatinine clearance of 70 mL/min, 1.46; for a creatinine clearance of 50 mL/min, 2.25; for a creatinine clearance of 30 mL/min, 3.70; and 8.91 for patients undergoing dialysis). In a prospective cohort study from the Northern New England Cardiovascular Disease Study Group of patients after coronary artery bypass grafting surgery (CABG), the presence of dialysis-dependent CKD was associated with a 4-fold increase in hospital mortality rate compared with patients not undergoing dialysis (12.2% vs 3%; adjusted odds ratio for death of 3.1). Thus, these epidemiologic studies demonstrate that CKD is a highly prevalent condition in which varying degrees of CKD are associated with mortality and cardiovascular events and higher morbidity after interventions for cardiovascular diseases. Prevention of renal disease and better treatments for cardiovascular disease in patients with established CKD will likely have a significant impact on survival rates.
Defining CKD

Chronic kidney disease is defined according to the presence or absence of kidney damage and level of kidney function—irrespective of the type of kidney disease (diagnosis). Among individuals with chronic kidney disease, the stages are defined based on the level of kidney function. Identifying the presence and stage of chronic kidney disease in an individual is not a substitute for accurate assessment of the cause of kidney disease, extent of kidney damage, level of kidney function, comorbid conditions, complications of decreased kidney function, or risks for loss of kidney function or cardiovascular disease in that patient. Defining stages of chronic kidney disease requires “categorization” of continuous measures of kidney function, and the “cut-off levels” between stages are inherently arbitrary. Nonetheless, staging of chronic kidney disease will facilitate application of clinical practice guidelines, clinical performance measures and quality improvement efforts to the evaluation, and management of chronic kidney disease (Table 1).16

Using serum creatinine level as an indicator of renal function grossly underestimates the prevalence of renal insufficiency. Even the use of equations to measure creatinine clearance may underestimate the prevalence of CKD, especially in the elderly.16,17 (Table 1) The prevalence of CKD is severely underestimated when it is defined on the basis of serum creatinine level instead of creatinine clearance. (Fig. 7).18,20

Small rises in creatinine are linked to poor long-term outcomes

Recently, it has been shown that even mild degrees of kidney disease translates to differences in outcomes after coronary artery disease.21-24 The leading theory is that when renal function declines, the associated abnormal pathobiology accelerates, and hence the progression of CVD events occurs at a higher rate.25 In adults in the Multiple Risk Factor Intervention Trial (MRFIT), even a mild increase in creatinine level was an independent risk factor for coronary heart disease and all-cause mortality.26 Recently, the Heart Outcomes Prevention Evaluation (HOPE) trial investigators demonstrated a 40% increase in the risk of major adverse cardiovascular events associated with mild CKD (creatinine level 1.4–2.3 mg/dL).27 Additionally, a GFR <75 mL/min/1.73 m² was an independent predictor of mortality in both ST elevation and non-ST–elevation myocardial infarctions.28 (Fig. 8) Greater degrees of CKD are associated with increased adverse outcomes after cardiovascular events, and in elderly patients with mild CKD (creatinine level, 1.5–2.4 mg/dL), the 1-year mortality rate was nearly doubled compared with elderly patients with normal renal function (46% vs 24%).28,29 Moderate CKD (creatinine level, 2.5–3.9 mg/dL) resulted in an even higher mortality rate of 66%. Thus, CKD is a strong predictor of mortality after a myocardial infarction.

Changes with aging

![Fig. 7. Percentiles of GFR and Cockcroft-Gault Ccr by age plotted on the same graph as data by Davies and Shock on insulin clearance in healthy men. Percentiles are calculated using a fourth-order polynomial weighted quantile regression. The solid line shows a polynomial regression to the insulin data. Dashed lines without symbols show the 5th and 95th percentiles for GFR estimates. (Reproduced with permission from Coresh, J, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003 41:1-12.)](image)

Table 1: Definition and stages of chronic kidney disease

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73m²)</th>
<th>With kidney damage</th>
<th>Without HBP</th>
<th>With HBP</th>
<th>Without HBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>1</td>
<td>1</td>
<td>High blood pressure</td>
<td>Normal</td>
</tr>
<tr>
<td>60-89</td>
<td>2</td>
<td>2</td>
<td>High blood pressure With ↓ GFR</td>
<td>↓ GFR</td>
</tr>
<tr>
<td>30-59</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>15-29</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>&lt;15 (or dialysis)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Shaded are represents chronic kidney disease; numbers designate stage of chronic kidney disease.

*Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
** High blood pressure is defined as ≥ 140/90 in adults and > 90th percentile for height and gender in children.
^ May be normal in infants and in the elderly.
The presentation of cardiovascular disease in elderly patients is complicated by its superimposition on the physiologic and structural cardiovascular changes of aging, which decreases cardiac functional reserve capacity, limits the performance of physical activity, and lessens the ability to tolerate a variety of stresses, including cardiovascular disease. These changes and their possible relationship to atherosclerosis are described in Table 2 and Table 3. These myriad changes require that the cardiovascular manifestations of aging be differentiated from those of disease.

There is a growing body of evidence that increased large artery thickening and stiffness and endothelial dysfunction in apparently otherwise healthy older persons and the ensuing increase in systolic and pulse pressure, formerly thought to be part of "normal" aging, precede clinical disease and predicts a higher risk for developing clinical atherosclerosis, hypertension, and stroke. There is also evidence of a vicious cycle: altered mechanical properties of the vessel wall influence the development of atherosclerosis, and the latter, via endothelial cell dysfunction and other mechanisms, influences vascular stiffness. Combinations of age associated endothelial dysfunction, intimal medial thickening, arterial stiffening, and arterial pulse pressure widening occurring to varying degrees determine the overall vascular aging profile of a given individual. Additional risk factors - including hypertension, smoking, dyslipidemia, diabetes, diet, kidney disease and heretofore unidentified genetic factors - interact with vascular aging (as described above) to activate an atherosclerotic plaque. According to this view, the development and progression of atherosclerosis in older persons differs from that in younger persons and from that in experimental younger animals because it represents an interaction of atherosclerotic risk factors and their effect to produce atherosclerotic plaque at any age and related to vascular aging.

Cardiorenal disease

The modern day, first world epidemics of obesity and hypertension are central drivers of a secondary epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD). Approximately half of those with diabetes will develop diabetic nephropathy. Conversely, half of all cases of end-stage renal disease (ESRD) are due to diabetic nephropathy. With the graying of America, and cardiovascular care shifting towards the elderly, there is an imperative to understand why decreasing levels of renal dysfunction act as a major adverse prognostic factor after contrast exposure with or without peripheral or percutaneous coronary intervention (PCI).

A 45–54-year-old dialysis patient has a cardiovascular mortality risk about 65 times higher than the general population. A 3-fold increased risk is detectable in patients even with very mild increases in serum creatinine. Thus, the risk rises steeply as renal failure progresses. It is useful to start with the final outcome, ESRD, when trying to determine the dynamics of its risk factors. The predicted risk of death from cardiovascular disease in the next 5 years for a 50-year-old smoker with a previous myocardial infarction, a systolic BP of 140 mmHg and serum cholesterol of 190 mg/dl is 5.4%. The predicted risk would be 50% (almost 10 times higher) if the man is on chronic dialysis treatment. This huge difference in risk suggests that, in patients with ESRD, traditional risk factors only partly account for the high cardiovascular mortality rate. In recent years, substantial progress has been made in identifying risk factors specific to patients with uraemia. Anaemia, extracellular volume expansion, inappropriately increased angiotensin II levels, high calcium-phosphate product (Ca/P), inflammation, hyperhomocysteinaemia, and, perhaps, impaired nitric oxide (NO) synthesis, due to accumulation of NO synthase inhibitors, all contribute to cardiovascular risk in ESRD. Most of these factors affect generation of reactive oxygen species. It appears likely that high oxidative stress plays an important role in mediating adverse effects on the cardiovascular system. Genetic factors, such as gene polymorphisms that regulate homocysteine levels, the renin-
Table 2. Cardiovascular structural remodeling

<table>
<thead>
<tr>
<th>Age-associated changes</th>
<th>Plausible mechanisms</th>
<th>Possible relation to human disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>▲ Vascular intimal thickness</td>
<td>▲ Migration of and ▲ matrix production by VSMC Possible derivation of intimal cells from other sources</td>
<td>Promotes development of atherosclerosis</td>
</tr>
<tr>
<td>▲ Vascular stiffness</td>
<td>▲ Elastin fragmentation ▲ Elastase activity ▲ Collagen production by VSMC and ▲ Cross-linking of collagen Altered growth factor regulation/tissue repair mechanisms</td>
<td>Systolic hypertension Left ventricular wall thickening Atherosclerosis Stroke LVH ??</td>
</tr>
<tr>
<td>▲ LV wall thickness</td>
<td>▲ LV myocyte size with altered Ca(^{+}) handling ▲ Myocyte number (necrotic and apoptotic death) Altered growth-factor regulation Focal matrix collagen deposition</td>
<td>Retarded early diastolic cardiac filling ▲ Cardiac filling pressure Lower threshold for dyspnea ▲ Likelihood of heart failure with relatively normal systolic function LVH ??</td>
</tr>
<tr>
<td>▲ Left atrial size</td>
<td>▲ Left atrial pressure/volume</td>
<td>▲ Prevalence of atrial fibrillation and other atrial arrhythmias</td>
</tr>
</tbody>
</table>

Table 3. Cardiovascular functional changes

<table>
<thead>
<tr>
<th>Age-associated changes</th>
<th>Plausible mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered regulation of vascular tone</td>
<td>▲NO production/effects</td>
</tr>
<tr>
<td>Reduced threshold for cell Ca(^{+}) overload</td>
<td>Changes in gene expression of proteins that regulate Ca(^{+}) handling; increased ω6:ω3 polyunsaturated fatty acids ratio in cardiac membranes</td>
</tr>
<tr>
<td>▼ Cardiovascular reserve</td>
<td>▲Vascular load ▼ Intrinsic myocardial contractility Ventricular-vascular load mismatch during stress ▲ Plasma levels of catecholamines ▼β-adrenergic modulation of heart rate myocardial contractility and vascular tone due to postsynaptic signaling deficits</td>
</tr>
</tbody>
</table>

angiotensin system and the endogenous anti-oxidant system itself, are all important also. Furthermore, an absolute or relative deficiency in anti-oxidants such as vitamin C or E, or other endogenous vasoprotectors such as adiponectin, may contribute to vascular damage.\(^{37,38}\)

**Pathobiology of atherosclerosis**

Atherosclerotic lesions (atheromata) are asymmetric focal thickenings of the innermost layer of the artery, the intima (Fig. 10). These consist of cells, connective-tissue elements, lipids, and debris.\(^{39}\) Blood-borne inflammatory and immune cells and their derivatives constitute an important part of an atheroma, the remainder being vascular endothelial and smooth-muscle cells. The atheroma is usually preceded by a fatty streak, an accumulation of lipid-laden cells beneath the endothelium.\(^{40}\) Most of these cells in the fatty streak are macrophages, together with some T cells. Fatty streaks are prevalent in young people, never cause symptoms, and may
progress to atheromata or eventually disappear. The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries and can lead to ischemia of the heart, brain, or extremities, resulting in infarction. In the center of an atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of smooth-muscle cells and a collagen-rich matrix. T cells, macrophages, and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows.\textsuperscript{39-41} Many of the immune cells exhibit signs of activation and produce inflammatory cytokines.\textsuperscript{42-44}

The processes leading to the development of atherosclerotic lesion are not entirely clear. At least two hypotheses address the initiation of the disease: 'response to injury' and 'response to retention. The former is well supported by a large body of experimental evidence.\textsuperscript{45-47} Atherosclerosis is now generally considered an inflammatory disease - inflammation being the cause of both initiation and progression of the lesion.\textsuperscript{45, 46} Injury to endothelium may be the important event that begins the atherosclerotic process. This injury could be due to elevated blood cholesterol levels, hypertension or other factors such as local infections, smoking. Several types of lipid particles can contribute to the formation of fatty streaks, including cholesterol rich low density lipoprotein particles (LDLs) and triglyceride rich VLDL and remnant particles. Retained lipoproteins tend to get oxidized and become pro-inflammatory and induce further oxidative stress in the surrounding vascular cells (below) leading to recruitment monocyte-macrophages into the subendothelial space and intima and migration of advential smooth muscle cells to intima and their subsequent proliferation within the intima. (Fig 11, 12)

Atherosclerotic lesions are considered advanced when associated with accumulations of lipid, cells (macrophages and smooth muscle cells), and certain matrix components such as collagens and chondroitin sulfate proteoglycans. Proliferation of smooth muscle cells initially may be advantageous since it will generate a fibrous cap to stabilize the lesions. However unregulated proliferation of smooth muscle cells leads to complications as shown in animal models of atherosclerosis and balloon angioplasty-induced restenosis. Lesions considered advanced by their histology may not necessarily narrow the arterial lumen or produce clinical manifestations. This may be due to the fact that these areas covered by a monolayer of endothelial cells or certain matrix components such as heparan
sulfate proteoglycans that provide an anti-thrombotic surface over the plaque. Loss of endothelium or heparan sulfate proteoglycans may uncover sub-endothelial collagen providing a pro-thrombotic surface that promotes platelet adhesion and activation. Thrombosis is a major contributor to complication of atherosclerosis. There are two major causes of coronary thrombosis: plaque rupture and endothelial erosion. Plaque rupture, which is detectable in 60 to 70 percent of cases, is dangerous because it exposes prothrombotic material from the core of the plaque — phospholipids, tissue factor, and platelet-adhesive matrix molecules — to the blood. Ruptures preferentially occur where the fibrous cap is thin and partly destroyed. At these sites, activated immune cells, which are abundant, produce numerous inflammatory molecules and proteolytic enzymes that weakens the cap and activates cells in the core, transforming the stable plaque into a vulnerable, unstable structure that can rupture, induce a thrombus, and elicit an acute coronary syndrome. Myocardial infarction occurs when the atheromatous process prevents blood flow through the coronary artery.

Thus, in summary, at least three key processes contribute to the complications of atherosclerosis inflammation, cell proliferation and thrombosis (Fig. 13). While cytokines and oxidative stress contribute to inflammation, mitogens and degradation of specific matrix components may contribute to unregulated smooth muscle cell proliferation and thrombosis. It is now evident that the activation of plaque rather than stenosis precipitates coronary ischemia and infarction.

**Atherosclerosis in patients with kidney disease**

The etiology of cardiovascular disease in CKD is complex and may result from an increased prevalence of classic cardiovascular risk factors and factors unique to uremia or dialysis (Table 3). As approximately 40% of patients undergoing dialysis have diabetes mellitus as their stated etiology for ESRD and 25% of patients undergoing dialysis have hypertension as their stated etiology for ESRD, patients with CKD have a higher prevalence of the cardiovascular risk
factor compared with the general population. CKD may also have an added effect with classic cardiovascular risk factors such as diabetes mellitus. In the Bypass Angioplasty Revascularization trial, at 7 years of follow-up, the survival rate was highest in patients who had neither CKD or diabetes mellitus (88%) and decreased with either (CKD:61%; diabetes: 72%). However, when both conditions were present, the survival rate was only 33%. The increased presence of classic cardiovascular risk factors does not fully account for the marked increased risk of cardiovascular events seen in patients with CKD. This may be related to potential unique mechanisms of accelerated atherogenesis in CKD, which may relate dialysis or to the uremic state itself. These are discussed below. (Table 4)

CKD may be a unique cardiovascular risk factor. Atherosclerosis in CKD is associated with some distinctive histologic features of degenerative changes within the media of the coronary arteries, calcification and proteoglycan accumulation, and a lack of lipid accumulation. In animal models, uremia enhances atherogenesis. Moreover, in children undergoing dialysis, coronary artery disease develops proportionally to the duration of dialysis. The uremic state itself can be associated with specific additional risk factors (volume overload, calcium-phosphorus abnormalities, increased oxidative stress, hypercatabolism, undefined uremic toxins) which may contribute to the development and progression of atherosclerosis. A chronic inflammatory state and the accumulation of metabolic products such as AGE and ADMA certainly play a major role. Chronic inflammation may be related to concomitant diseases such as diabetes mellitus, recurrent infections and the effects of chronic dialytic therapy. Pro-inflammatory cytokine levels (IL-6, CRP, IL-1, TNF-α, MCP-1) are increased in predialysis and dialysis patients. However, the levels of these cytokines and acute phase proteins rise significantly when patients are treated by HD.

Extracorporeal circulation of blood during HD may act as a repeated stimulus for an inflammatory response, mainly due to: i) exposure of circulating mononuclear cells to the dialysis membrane, ii) exposure of circulating blood to lipopolysaccharide on the dialysate site of the membrane, iii) membrane bio-incompatibility, iv) back-filteration of bacteria-derived contaminants, v) type of vascular access, or vi) unrecognized infections.

These findings suggest that non-traditional risk factors for CVD may be especially applicable in the ESRD population and in patients with CKD and are likely to be significant contributors to CVD progression. When ESRD is treated with renal transplantation, the risk of future cardiovascular events decreases despite the baseline high-risk population. Thus, kidney disease itself may have a direct role in atherogenesis and subsequent cardiovascular events. In addition to it’s direct role in affecting atherogenesis, kidney disease also worsens alters other known traditional and non traditional risk factors

Table 4. Risk Factors for Atherogenesis associated with kidney disease

<table>
<thead>
<tr>
<th>Lipid Abnormalities:</th>
<th>↑lipoprotein a; ↓HDL and ↑ triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension:</td>
<td>Kidney disease and ESRD cause hypertension by many mechanisms, predominantly volume overload</td>
</tr>
<tr>
<td>Diabetes Mellitus:</td>
<td>↑prevalence in CKD, as it is a common cause for CKD</td>
</tr>
<tr>
<td>Inflammation and oxidative stress:</td>
<td>↑in CKD, though exact pathogenesis unknown. Inflammation is an integral part of atherogenesis, in part due to ↑ oxidative stress. CKD is associated with ↑ monocyte activation, ↑ cytokines associated with inflammation. Oxidative stress enhances atherosclerosis, in part by activating monocytes, promoting inflammation, ↑ LDL oxidation with ↑ cellular uptake, thus ↓ NO bioavailability leading to endothelial dysfunction</td>
</tr>
<tr>
<td>Hyperhomocysteinemia:</td>
<td>↑ in CKD due to ↓ folate and vitamin B intake and ↓ renal clearance of Hcy. Hcy ↑oxidative stress, ↑ free lipoprotein (a), ↑ platelet adhesion and ↓ fibrinolysis which may promote atherogenesis</td>
</tr>
<tr>
<td>Fibrinogen:</td>
<td>↑ in CKD leading to a procoagulable state and predicts CAD in these patients</td>
</tr>
<tr>
<td>Nitric Oxide:</td>
<td>Bioavailability ↓ in CKD, leading to endothelial dysfunction and promote atherogenesis</td>
</tr>
</tbody>
</table>
for atherosclerosis. Some of these are discussed below.

1. Hyperlipidemia

In patients with CKD, lipids are more atherogenic, even when their levels are not elevated. Hypertriglyceridemia is common early in the development of CKD, and may be caused by decreased high-density lipoprotein cholesterol (HDL)-mediated cholesterol clearance and inhibition of lipolysis. Later in the progression of CKD, HDL and plasma lipoprotein lipase activity is decreased and may contribute to hypertriglyceridemia. In patients undergoing dialysis, an unfavorable lipid profile, specifically a low HDL cholesterol level and a high triglyceride concentration, is associated with rapid progression of coronary calcification on serial electron-beam computed tomography. Thus, multiple mechanisms, including insulin-resistance and inhibited activity of lipoprotein lipase, may contribute to hypertriglyceridemia in CKD. Besides being a risk factor of atherosclerosis, lipid profiles are also a marker for malnutrition. A low serum cholesterol concentration or evidence of malnutrition as indicated by other markers is associated with enhanced mortality in patients with CKD. In patients who are malnourished and have severe CKD but are not yet undergoing dialysis, plasma Lp(a) levels were higher than in patients who were not malnourished. Additionally, a significant direct relationship between CRP and plasma Lp(a) was found, and levels of both CRP and Lp(a) were elevated in patients with moderate to severe malnutrition. These data suggest that inflammation may be more prevalent in patients who are malnourished and may help to explain why in clinical practice, hyperlipidemia does not appear to be significantly associated with CKD. Considerable attention is now being paid to this “malnutrition-inflammation-atherosclerosis” axis. The bimodal distribution of cardiovascular events with both low and high cholesterol concentrations may mask the true role of lipid reduction in the development of coronary disease in patients with CKD. It has recently been shown that Apolipoprotein E (APOE) genetic variation predicts chronic kidney disease progression, independent of diabetes, race, lipid, and nonlipid risk factors. Risk is lower for those with the ε 4 allele and may increase with ε 2, consistent with previous diabetic nephropathy studies, and the risk is of comparable magnitude but in the opposite direction to the association of APOE with CHD.

2. Inflammatory and oxidative stress

Oxidative stress involves the increased production of oxygen free radicals, which can exhaust endogenous antioxidants and lead to vascular injury. ESRD increases oxidative stress, a key mechanism in the development of endothelial dysfunction and atherosclerosis. Oxygen free radicals activate monocytes and promote inflammation, an integral component to atherosclerotic plaque formation and plaque rupture. Patients undergoing dialysis, levels of both F2-isoprostanes, a marker of in-vivo oxidative stress, and CRP are elevated. Increased levels of CRP (>16.8 mg/L) are associated with a mortality rate that is twice as high as that in patients with low levels of CRP. Increased oxidative stress impairs nitric oxide bioavailability, which has a critical role in maintaining vascular tone and inhibiting atherosclerosis. CKD is also associated with decreased basal whole body nitric oxide production. Thus, oxidative stress, diminished nitric oxide bioavailability, and inflammation may all contribute to the development of atherosclerosis in patients with CKD.

3. Hyperhomocysteinemia

CKD increases the frequency and severity of hyperhomocysteinemia, which is independently associated with cardiovascular events and mortality. Hyperhomocysteinemia has many causes in CKD, including decreased activity of the remethylation cycle, decreased serum folate and B vitamin intake, and decreased renal clearance of homocysteine and cysteine. Homocysteine may increase oxidative stress, decrease nitric oxide availability, and produce endothelial dysfunction. Hyperhomocysteinemia is also associated with increased levels of Lp(a), an inhibitor of the fibrinolytic system, and enhances platelet adhesion to the vascular wall, and therefore could theoretically be a central factor in the development of coronary artery disease in CKD. Although an association between homocysteine levels and cardiovascular events has been proven, particularly in patients with CKD, causality has not yet been established.

4. Fibrinogen

Fibrinogen is a marker for adverse cardiovascular events in patients with stable angina and in patients who have sustained an acute myocardial infarction. CKD is associated with elevated levels of fibrinogen. Fibrinogen is required for platelet aggregation through its interaction with the glycoprotein IIb/IIIa receptors and can also be cleaved to fibrin, an essential step in blood clot formation. Fibrinogen crosslinks with Lp (a) and is co-localized within atherosclerotic plaques, leading to local degradation of fibrinogen to fibrin and enhancement of local coagulability.

5. Malnutrition

Malnutrition, which is common in ESRD, is prevalent both in dialysis and predialysis patients and may be associated with increased cardiovascular mortality in HD patients. Reduced levels of albumin or prealbumin, usually an indicator of malnutrition, are predictors of all-causes mortality as well as cardiovascular mortality in dialysis patients. Hypoalbuminemia may be explained by reduced synthesis, a consequence of the pro-inflammatory state. Many cytokines (especially TNF-α and IL-6) also suppress appetite and induce catabolism, leading to a wasting illness that may be indistinguishable from malnutrition. Stenvinkel et al showed that malnutrition is closely associated with the prevalence of atherosclerosis (evaluated as the presence of unilateral or bilateral carotid plaques) and the inflammatory response. This interaction between malnutrition and atherosclerosis might be partially explained by the increased inflammatory stimulus in ESRD patients, and these overlapping conditions probably underlie the accelerated progression of CVD in ESRD.
6. Vascular calcifications

Vascular calcification potentially is a different process in those patients with ESRD compared to those with normal renal function. The calcification in ESRD is thought to occur at two sites in the vessel wall: in the media where it is known as Monckeberg’s sclerosis (occurs initially in the media of the vessel, usually at the internal elastic lamina, and is not associated with lipid-laden macrophages and intimal hyperplasia, and in the intima (typically found in large vessel disease and coronary arteries, and associated with lipid-laden macrophages and intimal hyperplasia), where it is invariably associated with atherosclerosis.100 Cell biology studies suggest coronary artery calcification (CAC) is an active process analogous to bone formation, given that several genes expressed by calcifying vascular smooth muscle cells are also expressed by osteoblasts.191, 192 Most analyses so far specifically demonstrate that calcium, phosphorus, CPP, and PTH levels, whether measured in cross-section or longitudinally, are not related to CAC or its progression. While high levels of CAC almost certainly represent significant CAD in patients with ESRD, the attenuation of progression of CAC and its relation, if any, to CAD event reduction is unknown.193

7. Anemia and erythropoietin therapy

Anemia is common in CKD in patients undergoing dialysis and in the period before dialysis. At the time of initiation of hemodialysis, 29% of patients are receiving recombinant erythropoietin therapy.103 Even in patients with mild CKD who have a serum creatinine level <2 mg/dL, 45% of patients had a hematocrit level <36%.104 In patients undergoing dialysis, there are multiple studies demonstrating a strong association between hematocrit level and survival.105-107 In a study of 21, 899 patients undergoing dialysis, a hemoglobin level <8 mg/dL was associated with a doubling of the mortality rate.108 The increased mortality rate associated with anemia is primarily caused by cardiovascular causes, which may relate to the association with left ventricular hypertrophy (LVH).109 Treatment of anemia may be a modifiable factor in the high cardiovascular mortality and morbidity rates of patients with CKD.

Treatment of acute and chronic coronary artery disease

Patients with CKD clearly constitute a high-risk group for cardiovascular disease and cardiac death.29 Therefore both primary and secondary prevention of coronary disease is essential in such patients. However, because of certain possible differences in the mechanism of atherosclerotic and thrombotic disease between patients with and patients without CKD, an increased risk of certain therapies in patients with CKD, and a lack of data on therapeutic outcomes in such patients, it is unclear whether treatment strategies for primary and secondary prevention designed for the general population are safe and effective for patients with CKD.

Treatment strategies

In addition to treatment of clinical manifestation of atherosclerosis, some effort is now being directed towards prevention and treatment of atherosclerosis, in patients with and without kidney disease. Although LDL lowering, diabetes and blood pressure control help in managing the disease, there is a dire need for direct disease modifiers. Some of the more promising strategies are:

1. Lipid Modulation

LDL lowering

Cholesterol-lowering drugs, the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (statins), can achieve a relatively large reduction of plasma cholesterol. Clinical trials have demonstrated that statins can reduce of cardiovascular-related morbidity and mortality.110 It is generally assumed that the beneficial effect of statins on coronary events is linked to their hypcholesterolemic properties. However, potential pleiotropic effects are now being understood; hence, effects other than cholesterol reduction may play a role in the anti-atherosclerotic properties of statins.

Non-LDL lipid modulation

HDL can be atheroprotective in several ways.111,112 HDLs can counteract the effects of LDL by removing cholesterol, by a process termed reverse cholesterol transport, from cells in the arterial intima. HDL has antioxidant properties and inhibits LDL oxidation and oxidized LDL-induced adhesion and migration of monocytes. HDL also modulates endothelial function probably by stimulating endothelial NO production an important anti-atherogenic molecule.

Moderate HDL elevation (5-30%) can be achieved by niacin, fibrates and some statins. Niacin stimulates the synthesis of apoA-I and apoA-II and is by far the most effective HDL elevator (up to 30%). Clinical trials of ETC-216 (Esperion), which contains a phospholipid plus recombinant ApoAI Milano, a variant of the naturally occurring apoA1 on patients with acute coronary syndromes showed a 4% but statistically significant reduction in plaque volume.

HDL particles are subject to continuous remodeling in plasma. Two proteins in particular are emerging as pharmacological targets for HDL elevation by targeting this remodeling: ATP-binding cassette Al (ABCA1) and cholesteryl ester transfer protein (CETP).113,114

ACAT inhibitors

Acyl-CoA:cholesterol acyltransferase (ACAT) is involved in cholesterol metabolism in macrophages, liver, intestine, and adrenal cortex and may be involved in the development of atherosclerotic lesions.115 The presence of cholesteryl ester-enriched macrophages (foam cells) is a characteristic finding within atherosclerotic lesions. ACAT plays a pivotal role in foam cell formation converting free cholesterol to esterified cholesterol.

Eflicumibe and Pratimibe are ACAT inhibitors under development and undergoing trials at various clinical stages.

2. Inflammation and atherosclerosis

There are at least two such approaches that are in clinical development.

AGI-1067

AGI-1067 is antioxidant that is closely related to the
Antioxidant probucol discovered in 1960.

AGI-1067 exhibits greater water solubility and cell permeability compared with probucol, and inhibits inducible VCAM-1 expression in vascular endothelial cells. The nonintervened reference coronary segments of the PCI vessel demonstrated improvements with AGI-1067 in the Canadian Antioxidant Restenosis Trial-1 (CART-1), a double-blind, placebo-controlled, randomized trial of 305 patients; evidence supportive of a clinical effect on slowing atherosclerosis progression. This compound is currently in trials for atherosclerosis.

**BO-653**

BO-653 is a novel antioxidant (2,3-dihydro-5-hydroxy-2,2-dipentyl-4,6-di-tert-butylbenzofuran, Table 1), related to cc-tocopherol and probucol but with superior antioxidant properties, and is currently being investigated.106,107

**Lp-PLA2 inhibitors**

Lipoprotein-associated phospholipase A2 (Lp-PLA2, also known as platelet activating factor (PAF)-acyethylhydrolase) is a lipase associated with LDL in human plasma. Lp-PLA2 inhibition is an anti-inflammatory strategy considered for atherosclerosis.108 It hydrolyzes oxidized phosphatidylcholine (PC) to lyso-PC and oxidized fatty acids. These products are pro-inflammatory and implicated in monocyte recruitment and plaque development. The relevance of Lp-PLA2 to atherosclerosis is a subject of debate, and recent results suggest that the LDL-associated Lp-PLA2 may be proatherogenic and distinct from that of the HDL-associated enzyme. Lp-PLA2 has been shown to be a risk factor for coronary events in both men and women.109 SB480848 is currently in late clinical trials for atherosclerosis.

**Antiproliferative/cytotoxic agents for drug eluting stents**

Prevention of restenosis after successful angioplasty remains one of the most challenging issues in the treatment of obstructive coronary artery disease. The mechanism of in-stent restenosis consisted purely of neointimal smooth muscle cell proliferation. Several cell cycle regulators are being developed for restenosis. The two lead molecules are rapamycin and paclitaxel. Rapamycin (Sirolimus) is an antibiotic and immuno-suppressant, was shown to be a promising therapy for prevention of coronary artery stent restenosis.110,111 Rapamycin upregulates the cyclin-dependent kinase inhibitor p27kip1, resulting in cell-cycle arrest at the GI to S transition. The results obtained with rapamycin-eluting stents were dramatic (<5% restenosis) and were not observed with other therapeutic approaches. Paclitaxel an anticancer agent is another agent that is currently being developed for restenosis.112 Paclitaxel-eluting stents are now approved in Europe and Canada. Compounds like Sirolimus (e.g., everolimus, Guiudant/Novartis) are being pursued as next generation stent coating.

**Novel approaches for atherosclerosis/restenosis**

As outlined above, inflammation, smooth muscle proliferation and thrombosis are the major contributors to the disease process. These processes also contribute to the complications of restenosis and in-stent restenosis. Perlecain, a heparan sulfate proteoglycan present in the extracellular matrices of blood vessels may inhibit smooth muscle proliferation and thrombosis. Animal and human data show that there is a dramatic decrease in the content of heparan sulfate proteoglycans in atherosclerotic lesions.123,124 Multimodal targeting i.e., inhibition of smooth muscle cell proliferation, inflammation and thrombosis, can be achieved via induction of perlecain. Perlecain-inducing compounds inhibited both atherosclerosis and restenosis in animal models.

**Future directions**

Recent advances in our understanding of the age-associated alterations in vascular and cardiac structure and function, at both the cellular and molecular levels, and more attention being focused at kidney disease, provide valuable clues that will hopefully assist in directing future efforts to develop effective therapies to prevent, delay, or attenuate the CV changes that accompany aging.

Although CKD is highly prevalent in the United States and significantly contributes to the morbidity and mortality rate, there is still a paucity of clinical data on development of atherosclerosis, medications and outcomes in elderly patients with CKD. Fear of adverse effects and adverse events in this population may be driving the absence of these data.

Questions remain as to whether atherosclerosis and cardiovascular disease in patients with CKD is a fundamentally different process than in other patients. When treating patients with CKD, is it appropriate to follow the guidelines for the treatment of cardiovascular disease derived from large randomized studies in which patients with CKD were excluded? For example, data on the role of hyperlipidemia in the development of atherosclerosis in patients with CKD challenges the role of HMG CoA reductase inhibitors in this population. Unexpected results of clinical trials, including the adverse effect of normalizing the hemotocrit level in patients with CKD and the increased beneficial effects of ACE-I on coronary artery disease and congestive heart failure in patients with CKD, demonstrate the need for randomized clinical trials to determine the precise role for various medications in this population.27,125,126

Future advances in the prevention and treatment of cardiovascular disease in patients with CKD cannot occur until a more systematic approach is taken to study pharmacokinetics, accurately define the adverse-effect profile in this population, and expand the inclusion criteria of the larger efficacy studies to include these patients or design studies specifically targeting this population. Physicians must move beyond the apathy and frustration generated by treating patients with such a difficult disease process. Only by applying the same high standards of evidence-based medicine that have previously guided the treatment of atherosclerosis in the general population to elderly patients with renal dysfunction can we ever hope to improve the excessive mortality rates in these patients with CKD. Future guidelines and consensus statements are needed to help ensure...
consistent high-quality evidence-based care for the high-risk population of elderly patients with CKD.

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