Epidemiology and Mechanisms of Uremia-Related Cardiovascular Disease

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Abstract—Patients with chronic kidney disease and end-stage renal disease are at 5- to 10-fold higher risk for developing cardiovascular disease (CVD) than age-matched controls. Clinically, CVD in this population manifests as coronary artery disease, arrhythmias, stroke, or congestive heart failure. Beyond the traditional risk factors (eg, diabetes mellitus and hypertension), uremia-specific factors that arise from accumulating toxins also contribute to the pathogenesis of CVD. In this review, we summarize the literature on the epidemiology of both traditional and uremia-related CVD and focus on postulated mechanisms of the latter. In the context of current and emerging diagnostics and therapies for CVD, we highlight what we interpret as major gaps in the medical management of this growing population that need to be addressed with targeted epidemiological and translational research. Finally, we describe the global challenges associated with the recognition and management of uremia-related CVD in developed and developing nations. (Circulation. 2016;133:518-536. DOI: 10.1161/CIRCULATIONAHA.115.018713.)

Key Words: dialysis • heart diseases • kidney diseases • stroke

We must call attention to the cardiac symptoms.... Almost always death comes from uraemic accidents, which may assume two principal forms, pulmonary and cerebral. In the pulmonary form the patient is seized by paroxysmal dyspnoea, which comes especially at night, and which may be accompanied by pulmonary congestion, with expectoration of rust-colored sputum. This dyspnoea may lead to the death of the patient. The cerebral form is much more frequent. A number of patients show symptoms of cerebral apoplexy, together with hemiplegia, and die comatose.

P. Jousset, MD,1 describing common causes of death among patients with Bright disease

Chronic kidney disease (CKD) is an increasingly urgent public health concern that is projected to grow worldwide at a rate of 8% annually, with the fastest growth expected in developing nations.2,3 It has long been known that patients with kidney failure are predisposed to cardiovascular disease (CVD) that manifests clinically in various forms, including coronary artery disease, atrial or ventricular arrhythmias, myocardial infarction, stroke, or congestive heart failure. Over the last 30 years, it has become clear that the risk of CVD increases early in the course of progressive kidney disease and that the epidemiology, pathophysiology, prevention, and treatment of CVD and CKD are closely related and interdependent.4 In this review, we initially describe the epidemiology of CVD among people with CKD, noting the limitations of available research. We then discuss common risk factors for CVD (traditional and nontraditional) and key shared aspects of its pathophysiology with CKD. Next we describe emerging diagnostic tools and novel therapies that may help to delay or prevent end-stage renal disease (ESRD) and to curtail the escalating burden of cardiorenal disease. In the final section, we discuss the health services and health policy challenges that CKD and its inextricably linked CVD morbidities pose worldwide, particularly for low- and middle-income countries (LMICs).

Phenotypes and Epidemiology of CVD in Patients With CKD

Patients with CKD and some forms of CVD share a number of risk factors and underlying pathophysiological mechanisms that, by virtue of their similarities, offer opportunities to improve their management. The epidemiology of 4 of the commonest clinical phenotypes of CVD associated with CKD is discussed below.

Coronary Artery Disease
Coronary artery disease (CAD) is a leading cause of death among people with advanced CKD. Clinical syndromes compatible with CAD (including angina and myocardial infarction) are exceedingly common in patients with non-dialysis-dependent CKD, and the incidence of myocardial...
infarction increases at lower levels of estimated glomerular filtration rate (eGFR) and more severe albuminuria5,6 (Figure 1). Interpretation of the epidemiology of CAD is complicated by the frequent coexistence of CKD and diabetes mellitus because the latter is also a predisposing factor for cardiac events. However, even modest impairment of eGFR (without diabetes mellitus) is associated with an increased risk of myocardial infarction that is similar to or exceeds that associated with diabetes mellitus alone.7 Among people with both albuminuria and eGFR<45 mL·min⁻¹·1.73 m⁻², the rate of coronary events is substantially higher than that associated with diabetes mellitus alone (12.4 per 1000 person-years [95% confidence interval (CI), 9.7–15.9] versus 6.6 per 1000 person-years [95% CI, 6.4–6.9] respectively).8 The risk among people with both CKD and diabetes mellitus is comparable to that among people with prior coronary disease.8 Such findings have led to the suggestion that individuals with CKD (with or without diabetes mellitus) should be considered at very high risk of future coronary events.9

Unfortunately, acute coronary syndromes can be challenging to diagnose in people with severe CKD because chest pain and diagnostic electrocardiographic changes are less common than in the general population11 and because the prevalence of these clinical clues among people with acute coronary syndromes decreases in parallel with eGFR decline.11 For example, one study found that chest pain accompanied acute coronary syndrome among 44.4% of dialysis patients versus 68.3% in otherwise similar patients without a history of kidney failure.12 Cardiac troponin levels are more likely to be chronically elevated in people with kidney failure than in the general population,13 emphasizing the importance of searching for a temporally appropriate rise and fall of these biomarkers when considering the possibility of acute coronary syndrome.14

Existing epidemiological data related to CAD are limited by the considerations above and by the relatively poor predictive performance of exercise stress testing, radionuclide perfusion imaging, and stress echocardiography in people with advanced CKD.14-17 At least in the relatively healthier subset of patients with advanced CKD who are potential candidates for kidney transplantation, stress echocardiography appears to be associated with higher sensitivity and specificity for critical coronary disease than radionuclide perfusion imaging.15

Because of the known limitations of death certificate information,18 the true incidence and prevalence of CAD are uncertain, especially among patients with ESRD. Clearly, the case fatality rate after myocardial infarction is markedly elevated for both dialysis-dependent19 and non–dialysis-dependent6 CKD patients compared with people with normal kidney function.

### Ventricular and Atrial Arrhythmias

Sudden cardiac death (SCD) is defined as any sudden, unexpected death of cardiac cause, generally occurring without much (if any) warning. As others have noted,20 whether death is unexpected in dialysis patients given their very high burden of illness.

**Figure 1.** Relationships between cardiac events and loss of life expectancy resulting from cardiovascular disease (CVD) by stage of chronic kidney disease (CKD). A and B. The adjusted relative rate of all-cause mortality (ACM) and acute myocardial infarction as a function of glomerular filtration rate (eGFR; mL·min⁻¹·1.73 m⁻²) and severity of albuminuria as assessed by albumin-to-creatinine ratio (ACR; normal, ACR <30 mg/g; mild, ACR 30–300 mg/g; or heavy, ACR >300 mg/g). C and D. Adjusted loss of life expectancy resulting from CVD by CKD stage. Loss is compared with life expectancy in people with normal or mildly impaired kidney function (stage 1–2, eGFR ≥60 mL·min⁻¹·1.73 m⁻²) and normal or mildly increased albuminuria (stage 1, ACR< 30 mg/g). RRT indicates renal replacement therapy. C and D are reproduced from The Lancet, Gansevoort et al7 with permission from the publisher. Copyright © 2013, Elsevier.
can be difficult to ascertain. In clinical practice, determination of SCD requires either a witnessed collapse (with or without electrocardiographic evidence of serious ventricular arrhythmia) in an individual who subsequently dies or, after an unobserved death with no other obvious explanation, recent (ie, within 24 hours) observation of the decedent in his or her usual state of health. Anecdotally, because dialysis patients are known to be at high risk of heart disease, many unobserved deaths are attributed to SCD even though their true cause is unknown.

With recognition of these limitations, the proportion of deaths caused by SCD have been estimated at $\approx 20\%$ to $25\%$ among both hemodialysis and peritoneal dialysis patients. Some evidence of regional/ethnic variation exists. For example, the estimated proportion of SCD deaths among Japanese dialysis patients appears lower than in Western dialysis patients. SCD causes a substantial proportion of deaths even among adolescents and young adults with kidney failure, suggesting that nonischemic mechanisms may be responsible, as further described below. Accurately identifying SCD is less challenging in non–dialysis-dependent CKD patients, given their generally lower burden of comorbidity.

Multiple studies suggest that the likelihood of SCD is inversely proportional to eGFR, and one study in older patients found that even very mild impairment of kidney function (ie, eGFR $<60 \text{ mL·min}^{-1} \cdot \text{m}^{-2}$ [estimated with cystatin C but not creatinine]) was associated with an approximate doubling in the risk of SCD compared with those with normal eGFR. More information on the true incidence of unexpected deaths of cardiac origin would be extremely useful, as would precise electrocardiographic data on the type of cardiac rhythm responsible for death.

In patients with ESRD, episodes of supraventricular tachycardia (including atrial fibrillation) are common in the postdialysis period, although they are often self-limiting. In addition to transient episodes, persistent atrial fibrillation and paroxysmal atrial fibrillation are highly prevalent in hemodialysis populations (7%–27%, depending on the definition and cohort studied). Kidney failure is a major risk factor for atrial fibrillation, even after adjustment for age and comorbidity. As recently reviewed, the mechanisms underlying the elevated risk of atrial fibrillation in CKD patients include older age (with age-accompanying comorbidities such as hypertension and CVD), excessive inflammation, atrial and ventricular hypertrophy, activation of the renin-angiotensin pathway, and disorders of mineral metabolism. Reported estimates of the prevalence of atrial fibrillation in cohorts of non–dialysis-dependent CKD patients range from 8% to 18% compared with 0.4% to 1.0% in the population as a whole and $\approx 8\%$ among those $>80$ years of age. Atrial fibrillation can cause symptoms and increase the risk of iatrogenic complications, as described below. As in the general population, atrial fibrillation is a leading cause of stroke in patients with CKD. Thus, atrial fibrillation appears to make a substantial contribution to the high rate of CVD morbidity in CKD populations, although the magnitude of its contribution has yet to be precisely quantified.

**Stroke**

Stroke risk is elevated in those with non–dialysis-dependent CKD and is markedly increased in the presence of ESRD. The magnitude of this excess risk appears to be greater than that for CAD. For example, compared with those with normal kidney function, the relative risk of stroke in ESRD is 5- to 10-fold, whereas the relative risk of myocardial infarction in ESRD patients is 2.5- to 3-fold. Risk appears to be proportionately increased for both ischemic and hemorrhagic strokes, although there is some ethnic and racial variation. Cardioembolic strokes account for a relatively large proportion of ischemic strokes within the dialysis population, perhaps because of the increased prevalence of atrial fibrillation, as discussed above.

Risk factors for stroke in CKD patients largely mirror those in the general population: Diabetes mellitus, hypertension, and increasing age are all associated with higher-than-average risk, and black race is associated with lower risk. Available data in patients with ESRD do not convincingly support a temporal association between strokes and hemodialysis treatments. Stroke severity also tends to be higher among people with CKD compared with the general population, especially among those with kidney failure. At 30 days after stroke, mortality among dialysis patients in the United States approaches 30% compared with 10% to 13% in the general population. Furthermore, only 56% of US dialysis patients who suffer a stroke will be discharged home (or to acute rehabilitation).
Table 1. Five Subtypes of Cardiorenal Syndrome

<table>
<thead>
<tr>
<th>Cardiorenal Syndrome Type</th>
<th>Diagnosis</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Acute cardiorenal syndrome</td>
<td>Abrupt worsening of cardiac function (eg, acutely decompensated congestive heart failure) leading to acute kidney injury</td>
</tr>
<tr>
<td>II</td>
<td>Chronic cardiorenal syndrome</td>
<td>Chronic abnormalities in cardiac function (eg, chronic congestive heart failure) causing progressive and permanent chronic kidney disease</td>
</tr>
<tr>
<td>III</td>
<td>Acute renocardiac syndrome</td>
<td>Abrupt worsening of renal function (eg, acute kidney injury) causing acute cardiac disorder (acute heart failure)</td>
</tr>
<tr>
<td>IV</td>
<td>Chronic renocardiac syndrome</td>
<td>Chronic kidney disease (diabetic nephropathy) contributing to decreased cardiac function, cardiac hypertrophy, fibrosis, or increased risk of adverse cardiovascular events</td>
</tr>
<tr>
<td>V</td>
<td>Secondary cardiorenal syndrome</td>
<td>Systemic condition (eg, sepsis) causing both acute cardiac and renal injury and dysfunction</td>
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These cardiorenal syndrome types have been proposed by the Acute Dialysis Quality Initiative, as recently reported by McCullough et al. Reproduced with permission from the publisher. Copyright © 2013, S. Kargel AG.

compared with 72% to 76% for the general population. Potential explanations for these poor outcomes include the older average age of dialysis patients, frequent presence of comorbidities, delayed presentation to medical services, and possibly underuse of cardioprotective medications.

Congestive Heart Failure

The prevalence of left ventricular hypertrophy and congestive heart failure is higher among patients with CKD than in those without CKD. In the setting of severe kidney dysfunction, the signs and symptoms of heart failure can result from impaired renal excretion of salt and water, primary cardiac dysfunction (systolic or diastolic), or both. Thus, among patients with advanced CKD, a diagnosis of heart failure identifies a very heterogeneous group, and a functional classification system was recently proposed for use in this population. As for the other forms of CVD discussed in this review, the prevalence of heart failure in CKD populations increases with age, is inversely proportional to eGFR, is markedly more common in dialysis patients (prevalence, 31%–36%) than in those with normal kidney function (prevalence, 1.8%–4.4%), and is associated with poor prognosis. The presence of interstitial and perivascular fibrosis (Figure 2) in the heart is a major determinant of diastolic dysfunction among patients with CKD and hypertension. The simultaneous presence of heart and kidney failure has been called the cardiorenal syndrome. A detailed classification based on pathophysiology and clinical context has been proposed (Table 1).

Table 2. Traditional Risk Factors for CVD in Patients With CKD and Key Supporting Evidence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Epidemiological Evidence</th>
<th>Outcomes Evidence</th>
</tr>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Accounts for 45% of incident ESRD and is the most common cause of CKD.</td>
<td>Presence of CKD is strongly correlated with adverse outcomes, including all-cause mortality, acute myocardial infarction, stroke, and need for coronary revascularization. Approximately 30% of the projected $1.1 trillion cost of dialysis treatments during 2010–2020 will result from diabetic kidney disease.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>The prevalence of hypertension is significantly higher (50%–60%) in people with CKD than in the general population and rises to 90% in CKD patients age &gt;65 y of age.</td>
<td>Kidney dysfunction is a major cause of hypertension, and hypertension in turn aggravates CKD and accelerates its progression. Hypertension is the major risk factor for the development and progression of diabetic and nondiabetic CKD. CKD is a common and often underappreciated cause of resistant hypertension.</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Albuminuria is present in 9.5% of US adults.</td>
<td>Albuminuria is strongly and independently associated with multiple adverse outcomes, including death, cardiovascular events, and kidney failure.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Dyslipidemia is common among people with CKD (especially those with the nephrotic syndrome or treated with peritoneal dialysis).</td>
<td>Dyslipidemia appears to correlate with the rate of kidney function loss in CKD populations; however, it is unclear whether this association is causal. Some studies have shown a correlation between tobacco use and the risk and severity of albuminuria, but this has not been confirmed in all studies.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smokers are 1.5–3 times as likely to have CKD as nonsmokers.</td>
<td>Tobacco use accelerates kidney function loss once CKD is established.</td>
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above and beyond the traditional risk factors. Below, we focus our discussion on some novel factors that likely contribute to the pathogenesis of CVD.

**Protein Carbamylation**

Recent evidence suggests that chronically elevated blood urea may contribute directly to cardiovascular morbidity and mortality risk in CKD patients. As kidney function declines, accumulating urea spontaneously dissociates to form cyanate, which reacts irreversibly with proteins and free amino groups in a reaction known as carbamylation (Figure 4). Impaired acetylcholine-induced vasorelaxation has been observed in mice with urea levels comparable to those in uremic patients, suggesting that protein carbamylation may lead to uremia-related endothelial dysfunction. Carbamylated low-density lipoprotein has also been shown to markedly accelerate atherosclerosis and to reduce myocardial function in mice. Levels of carbamylated proteins provide a time-averaged indicator of urea concentration (analogous to the widespread use of hemoglobin A\textsubscript{1c} to indicate glycemic control in individuals with diabetes mellitus). Berg et al\textsuperscript{78} and Drechsler et al\textsuperscript{81} reported that higher levels of carbamylated albumin (C-Alb) are associated with a higher risk of all-cause mortality and uremic heart failure in both incident and prevalent ESRD populations. Koeth et al\textsuperscript{82} also demonstrated that increased concentrations for serum protein-bound homocitrulline (an alternative index of total protein carbamylation) was associated with cardiovascular risk in ESRD patients. Importantly, animal and human studies have suggested that protein carbamylation can be reversed by amino acid scavenger therapy.\textsuperscript{83}

Figure 3. Proposed feedback loops in cardiorenal syndrome. Cardiac dysfunction leads to renal dysfunction (green arrows) and vice versa (orange arrows). GFR indicates glomerular filtration rate. Adapted with permission of the publisher from Bock and Gottlieb. Copyright © 2010, Wolters Kluwer Health.

Figure 4. Carbamylation chemistry in uremia and the hypothesized pathogenic pathways.

- Atherosclerosis
- Cardiomyopathy
- Protein energy wasting/atrophy
Intensification of hemodialysis therapy also reduces protein carbamylation and may in part explain the benefits seen when dialysis dose (ie, frequency) is increased.

Protein carbamylation has thus emerged as a major pathogenic nontraditional risk factor among patients with CKD and ESRD and accordingly may be a promising target for intervention.

**Fibroblast Growth Factor-23–Klotho Signaling Axis**

Fibroblast growth factor (FGF)-23 is a protein secreted primarily by bone tissue that regulates phosphate excretion via interaction with classic FGF receptors. FGF23 signaling requires the presence of a coreceptor (Klotho). Human studies suggest that Klotho deficiency and increased FGF23 are hallmarks of CKD that are independently associated with cardiovascular mortality.

Klotho-deficient mice develop an accelerated aging syndrome with vascular calcification that resembles features of uremia. In Klotho-deficient mice, Faul et al demonstrated that high levels of FGF23 directly contributed to left ventricular hypertrophy by acting on noncanonical FGF receptors in the heart. FGF23 has also been shown to directly impair endothelium-dependent vasorelaxation by increasing vascular superoxide levels. Moreover, FGF23 regulates renal sodium absorption and may contribute to the hypertension that accompanies CKD. Neutralization of FGF23 in mouse models of CKD leads to decreases in secondary hyperparathyroidism but also to increases in serum phosphate and vascular calcification.

Secondary analysis of the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial in hemodialysis patients with secondary hyperparathyroidism (intact parathyroid hormone >300 pg/mL) demonstrated that FGF23 concentrations were reduced by ≥30% in 68% versus 28% of patients randomized to receive cinacalcet plus phosphate binders/vitamin D versus placebo plus phosphate binders/vitamin D, respectively. FGF23 concentrations were reduced by ≥50% in 50% versus 15% in patients randomized to cinacalcet versus placebo, respectively. By week 20, neutralization of FGF23 was associated with a significantly reduced risk of cardiovascular mortality, SCF, and heart failure and in the primary composite end point (ie, time to death or a first nonfatal cardiovascular event [myocardial infarction, hospitalization for angina, heart failure, or a peripheral vascular event]). Reductions in the risk of all-cause mortality, myocardial infarction, unstable angina, peripheral vascular event, stroke, fracture, and parathyroidectomy were not statistically significant.

**Vitamin D**

A number of observational studies in hemodialysis patients have suggested a survival advantage associated with activated vitamin D therapy. In various animal models, vitamin D supplementation has been shown to block the development of cardiac hypertrophy and heart failure. In the Dahl salt-sensitive rat model of heart failure, treatment with paricalcitol attenuated the development of cardiac hypertrophy and dysfunction as measured by functional, biochemical, and molecular measures of cardiac stress. These findings appear to be related directly to inhibition of renin production by calcitriol.

Other groups have demonstrated that cardiac hypertrophy in 1α-hydroxylase–deficient mice can be reversed by calcitriol but not by nutritional vitamin D and that cardiac-specific vitamin D receptor knockout mice develop cardiac hypertrophy. Small clinical studies in hemodialysis patients have demonstrated a role of vitamin D agonists in reducing left ventricular wall thickness and improving diastolic function parameters, although larger randomized trials in CKD have not. These larger trials have suggested that activated forms of vitamin D reduce left atrial size and potentially episodes of heart failure, which are interesting findings that warrant confirmation.

**Oxidative Stress**

Several animal and human studies have suggested that indicators of oxidative stress are markedly elevated in CKD. Because the kidney is one of the most important sources of antioxidant enzymes such as glutathione peroxidases, levels of pro-oxidants increase with worsening renal function. Urea itself has been demonstrated to induce reactive oxygen species in cell culture studies. Uremic mice have responded to treatment with antioxidants, showing improvements in both insulin resistance and vascular function. Iron therapy, frequently used to correct anemia in patients with CKD, may also induce oxidative stress. Iron is normally sequestered by proteins such as transferrin and ferritin. Because administration of intravenous iron may overwhelm the ability of these proteins to sequester iron, free (not protein bound) iron can be distributed in excess into tissues where its oxidative properties can be injurious. Free iron can react with hydrogen peroxide via the Fenton reaction to generate hydroxyl radicals. However, not all studies implicate iron as responsible for inducing oxidative stress of uremia, and perhaps differences in the way iron is measured (ie, total versus catalytic) explain the discrepancies. Whether the oxidative stress of uremia is a primary driver of CVD or a secondary phenomenon is unclear. Small randomized trials in ESRD patients have not shown any significant benefit of antioxidant treatment, suggesting that oxidative stress may not be a primary mediator of cardiovascular risk. Alternatively, targets and interventions that are more specific for uremia related oxidative stress should be studied.

**Cardiac Glycosides**

Endogenous cardiotonic steroids are another major class of metabolites that have been shown in small clinical studies to be significantly elevated (2- to 3-fold) in patients with CKD. These metabolites block Na/K-ATPase and include endogenous ouabain, marinobufagenin, and telocinobufagin. In animal models of CKD, cardiotonic steroids appear to induce myocardial dysfunction and fibrosis. Interestingly, monoclonal antibodies against marinobufagenin has also been shown to reverse cardiac fibrosis in rats with chronic renal failure. However, the exact role of cardiotonic steroids in mediating cardiovascular risk in CKD patients is unknown because no high-throughput, reliable assays are available to measure these metabolites in large cohorts of patients.

**Other Pathways**

The gut microbiome is emerging as an attractive candidate for investigation as a potential source of uremic toxins.
with CKD have altered gut microbiome patterns, and colonic bacteria are the main sources of several well-known toxins such as p-cresol sulfate, indoxyl sulfate, and trimethylamine-N-oxide. Recent studies have suggested that trimethylamine-N-oxide levels are elevated in patients with CKD and confer a nearly 3-fold excess risk for 5-year mortality. Circulating levels of asymmetrical dimethylarginine, an endogenous inhibitor of nitric oxide synthase, have also been implicated as an independent risk factor for CVD among patients with CKD. Some have speculated that the asymmetrical dimethylarginine pathway contributes to endothelial dysfunction and progression of atherosclerosis; however, treatment with sidelnail or l-arginine to restore impaired nitric oxide signaling has failed to reverse CVD. Finally, increased circulating levels of uremic solutes such as p-cresol sulfate and phenylacetylglutamine have been associated with higher cardiovascular morbidity and mortality in patient with ESRD, but it is not known whether removal or blocking these uremic toxins will lead to improved cardiovascular outcomes.

Current Management and Therapeutic Gaps

Coronary Artery Disease

Medical management of acute coronary events in patients with CKD has recently been reviewed by Washam et al. Supporting data in patients with CKD are extremely limited because randomized, clinical trials (RCTs) have not been conducted specifically to evaluate the benefit of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, heparin, thrombolytics, or immediate reperfusion strategies in this specific group. One systematic review using pooled RCT data to compare antplatelet agents with placebo in patients with CKD reported that the point estimate for the relative risk of myocardial infarction was consistent with a clinically relevant benefit of active treatment (relative risk=0.89; 95% CI, 0.76–1.05). However, the risk of major bleeding was significantly increased (relative risk=1.4; 95% CI, 1.07–1.86). The different pathophysiology of CVD in patients with renal disease, the increased risk of bleeding among people with advanced CKD, the need to dose adjust or to avoid low-molecular-weight heparins at lower eGFR, and the high case fatality rate after myocardial infarction among those with CKD all suggest the need for more trials comparing different approaches to treat acute myocardial infarction in this vulnerable population.

Slightly more data are available to guide long-term medical treatment of coronary disease in CKD patients. Antplatelet agents appeared to reduce the risk of myocardial infarction in 11,701 people with CKD (4398 with stage 5 CKD), some of whom had no history of coronary events (relative risk=0.66; 95% CI, 0.51–0.87), perhaps at the expense of excess major bleeding (relative risk=1.29; 95% CI, 0.69–2.42). Although treatment of hypertension reduces the risk of cardiovascular events in people with non-dialysis-dependent CKD, there is no specific cardiovascular benefit for more aggressive (eg, <130/80 mm Hg) compared with conventional (eg, <140/90 mm Hg) blood pressure targets and no evidence that any specific class of agent is preferred. Therefore, management of hypertension in non-dialysis-dependent CKD is tailored to the individual’s risk of progressive kidney function loss. Limited high-quality data are currently available to guide the treatment of hypertension in patients with ESRD.

Statins reduce the risk of coronary events in people with non-dialysis-dependent CKD, but there is no evidence that they are beneficial in the presence of ESRD. Because low-density lipoprotein cholesterol levels are poorly correlated with the risk of adverse clinical outcomes in CKD patients, overall cardiovascular risk, not the serum lipid profile, is now the primary basis for prescribing statins in this population. International guidelines recommend that statins be prescribed to all patients with non-dialysis-dependent CKD who are ≥50 years of age and to patients whose estimated 10-year risk of cardiovascular events exceeds 10%. The guidelines do not recommend initiating statins in dialysis patients, although patients who initiate dialysis while on a statin might reasonably continue such treatment.

No trial data support the cardiovascular benefits of exercise, dietary sodium restriction, avoiding overweight/obesity, or smoking cessation in CKD populations. However, dietary sodium restriction is useful (perhaps essential) for good blood pressure control in the setting of CKD. Tobacco use and overweight/obesity may accelerate kidney function loss. It is therefore appropriate, as with the general population, to recommend lifestyle changes to patients with CKD. However, important questions remain as to what extent such changes can be achieved.

Markedly worse outcomes after percutaneous or surgical coronary revascularization have been observed in patients with ESRD compared with individuals with normal kidney function. As a consequence of these studies, dialysis patients are less likely to receive coronary revascularization than those with normal kidney function. Recent studies are more optimistic and suggest a small net survival benefit of both surgical and percutaneous revascularization among dialysis patients and that surgical procedures are associated with better long-term survival than percutaneous revascularization, although at the expense of increased short-term morbidity and a higher risk of perioperative death. Similar considerations apply to patients with non-dialysis-dependent CKD.

Indications for coronary revascularization in CKD patients have yet to be evaluated in well-controlled studies, although a large RCT with a target enrollment of 1000 patients with coronary disease and eGFR <30 mL·min⁻¹·1.73 m⁻² or on dialysis is underway and will compare a routine invasive strategy with conservative management. No RCTs have specifically compared percutaneous and surgical methods for revascularization in people with CKD. A secondary analysis of data from a trial comparing percutaneous coronary angioplasty with surgical revascularization suggested that patency after the former might be less durable that with the latter among the subgroup with eGFR <60 mL·min⁻¹·1.73 m⁻². However, because this trial studied bare metal stents, its applicability to the current era is unclear.

Although the risk of postprocedural acute kidney injury (with the risk of permanent kidney failure) is a valid concern, observational studies of people with non-dialysis-dependent CKD suggest that there is net clinical benefit of revascularization because the risk of permanent dialysis is relatively
Sudden Cardiac Death
β-Blockers and mineralocorticoid receptor blockers (eg, eplerenone and spironolactone) reduced the risk of SCD in randomized trials of patients with heart failure.137-140 Whether these benefits also apply to the subset who also have advanced CKD is unknown. A small (n=114) RCT in hemodialysis patients with cardiomyopathy suggested that carvedilol reduced mortality141 but this requires confirmation in a larger study. A small (n=201) placebo-controlled RCT in hemodialysis patients suggested that n-3 polyunsaturated fatty acids reduced the rate of cardiovascular events.142 However, much larger RCTs of n-3 polyunsaturated fatty acid supplementation have shown no benefit in the general population.143 Accordingly, given the potentially different mechanisms for SCD (and the strong rationale for n-3 polyunsaturated fatty acid supplementation in severe CKD considering its higher likelihood of deficiency), a larger study is ongoing in hemodialysis patients.144

Implantable cardiac defibrillators (ICDs) are currently recommended for the primary prevention of SCD in people with severe heart failure.145 However, available data in non-dialysis-dependent CKD patients indicate that the clinical benefit of ICDs is reduced at lower eGFR (30–60 mL·min⁻¹·1.73 m⁻²).146 No RCT data support the use of ICDs in dialysis patients, and some evidence suggests that ICDs may be less effective in this population (ie, poorer outcomes despite more frequent shocks) and may be more likely to cause life-threatening infection than in those with normal kidney function.147 Limited data suggest that ICDs reduce the risk of death among dialysis patients with a history of cardiac arrest.148 A small trial (planned enrollment, n=200) is ongoing in dialysis patients who do not meet current criteria for ICD use but who appear to be at high risk of SCD,149 and a larger trial in patients undergoing incident dialysis (target enrollment, n=2600) that is powered for clinically relevant outcomes began recruitment in mid-2015.150

Atrial Fibrillation
Medical management of atrial fibrillation is divided into control of ventricular rate and rhythm (not discussed further except to note the well-known potential for digoxin toxicity in people with CKD) and prevention of cardioembolic events, including stroke. The usual approach to the latter among the general population is to estimate the risks of stroke or intracranial bleeding with validated equations151-156 and then use these estimates to select the appropriate treatment (ie, aspirin, warfarin, or other oral anticoagulants). Unfortunately, neither the performance of the validated equations nor the risk-to-benefit ratio of available treatments is completely understood in people with advanced CKD.

Which equation performs best for estimating stroke risk in CKD populations has been the subject of some debate. Most such equations do not incorporate eGFR (known to correlate with stroke risk), and none incorporate albuminuria (known to correlate with stroke risk in the general CKD population but not necessarily in the subset with atrial fibrillation).157-159 Although all 3 major equations for estimating bleeding risk incorporate information on kidney function, the relative performance of each within CKD populations is unknown.158-160

More research is needed to identify how best to predict stroke risk in people with atrial fibrillation and CKD, especially because the prevalence of both are expected to rise over the coming decades.

Aspirin appears to modestly reduce the risk of stroke among people with atrial fibrillation (general population), but to a lesser extent than warfarin.157,158 RCTs have yet to assess the benefits and harms of aspirin for stroke prevention in people with advanced CKD and atrial fibrillation, although RCTs have been recommended.159,160

Warfarin has long been the standard of care for most individuals (general population) with atrial fibrillation. This status has recently been challenged by the emergence of novel oral anticoagulants such as rivaroxaban, dabigatran, apixaban, and edoxaban. Warfarin use among patients with atrial fibrillation and advanced CKD currently enjoys less enthusiasm because of the relatively high bleeding risk in this population161 and the concern that warfarin might precipitate calciphylaxis, a devastating condition that affects a small number of patients on dialysis.162 Such concerns are particularly relevant because observational studies have shown no association between warfarin use and averted stroke in patients with severe CKD.163-165

Available data suggest that the efficacy of rivaroxaban, dabigatran, apixaban, and edoxaban is comparable to that of warfarin and that they can be safely used in people with stage 3 CKD. Rivaroxaban, dabigatran, and apixaban are approved for use in the United States in people with stage 4 CKD, and apixaban is approved for use in dialysis patients, all on the basis of pharmacokinetic data without any evidence of clinical efficacy or safety.165-169 A recent systematic review did not find that the newer agents were superior, but the point estimate for the risk of stroke was compatible with a substantial clinical benefit compared with warfarin despite a similar risk of bleeding (Figure 5).169-171 Additional trials are ongoing, and more information will soon be available.

Congestive Heart Failure
In general, CKD patients with heart failure and eGFR ≥30 mL·min⁻¹·1.73 m⁻² are treated the same as those with normal kidney function except that hyperkalemia may be more likely to limit doses of medications such as angiotensin-converting enzyme inhibitors or aldosterone antagonists.172-177 Reductions in eGFR reported in patients with heart failure treated with renin-angiotensin-aldosterone system inhibitors pose an additional concern that decline in renal function could be accelerated by these agents (by blocking renal autoregulation)178 and therefore limit their utility in this population. Patients with a eGFR of 15 to 30 mL·min⁻¹·1.73 m⁻² or with severe albuminuria may have increased diuretic requirements compared with
those with less severe CKD or with normal kidney function.175 Management of heart failure in the setting of advanced CKD can be broadly divided into 4 non–mutually exclusive objectives: preventing/controlling extracellular fluid (ECF) volume overload, optimizing cardiac function, preventing complications of heart failure (eg, CD) and treating the underlying disease. The last 2 objectives are not discussed further, and significant questions remain about how to achieve the first 2 objectives, especially in people with kidney failure.

Preventing/Controlling ECF Volume Overload
Management of heart failure in advanced CKD would be facilitated by better methods for routinely assessing ECF volume status. Current assessment of ECF volume status in this population is surprisingly crude. Promising techniques such as online blood volume monitoring,176 routine measurement of inferior vena cava diameter,177 noninvasive lung water measurement,178 lung ultrasound,179 and routine bioimpedance assessment180 remain understudied or can actually cause harm. Blood levels of brain natriuretic peptide correlate with left ventricular filling pressures in the general population and in people with non–dialysis-dependent CKD. A recent study suggests that amino-terminal pro-brain natriuretic peptide levels are useful for diagnosing heart failure, regardless of baseline eGFR.181 However, because brain natriuretic peptide appears to accumulate in the setting of kidney failure, regardless of baseline eGFR,181 further studies are required to clarify the role of brain natriuretic peptide assays to assess ECF volume status in CKD.

Even when ECF volume overload is correctly identified, how to best manage this condition poses unresolved challenges. Ultrafiltration to treat heart failure in patients with moderate CKD who lack a traditional indication for dialysis could exacerbate kidney dysfunction compared with diuretic treatment.185 For patients with kidney failure, quotidian hemodialysis appears effective186 but is not widely available. Better strategies are needed for coupling the rate and schedule of intradialytic fluid removal to each individual patient’s volume status and hemodynamic tolerance. Although moderation of dietary sodium intake and avoidance of excessive intradialytic fluid gains can effectively manage ECF volume overload, these objectives are often difficult for patients to achieve.

Optimizing Cardiac Function
Medications that antagonize the renin-angiotensin-aldosterone system such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, spironolactone, and eplerenone are all relatively unstudied in the presence of advanced CKD and heart failure. A single, small RCT suggested that telmisartan improved mortality in 332 hemodialysis patients (compared with placebo), but this result requires confirmation.187 A recently published subanalysis188 of the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) trial189 showed that the first-in-class angiotensin receptor neprilysin inhibitor (LCZ696) induced less eGFR decline than valsartan in patients with eGFR ≥30 mL·min−1·1.73 m−2. Provided that the LCZ696 data are reproduced in an RCT and further evaluated in patients with worse renal function, this agent might prove superior to other renin-angiotensin-aldosterone system inhibitors in CKD patients. Although in theory treating anemia in patients with CKD should improve cardiac function, epoetin therapy in this population has not improved cardiac outcomes or has caused harm.190–192 Randomized trials of cardiac resynchronization have not been carried out in people with advanced CKD, although subgroup analyses of CKD patients in larger trials suggest a mortality benefit with resynchronization.193

Stroke
The treatment of acute stroke in the general population continues to evolve, with increasing interest in catheter-based therapies.194–196 Data supporting the use of these newer treatments in patients with CKD or ESRD are scant. In theory, an increased likelihood of diffuse small-vessel disease and a higher prevalence of stiff, calcified cerebral blood vessels in CKD patients (especially in advanced CKD) may tip the risk-to-benefit balance to be less favorable, although this is speculative.20 The risk-to-benefit ratio of intravenous thrombolysis for acute stroke in CKD patients is similarly unknown compared with that in individuals with normal kidney function.197 Evidence for medical treatments aimed at preventing forms of ischemic stroke is broadly similar to the evidence base for prevention of acute coronary disease, although numerous gaps remain. Even fewer data are available on strategies to prevent hemorrhagic stroke. Gaps of particular importance related to ischemic and hemorrhagic stroke include the risk-to-benefit ratio of antiplatelet agents, the optimal blood pressure target (and how to achieve it, especially for dialysis patients), and how to mitigate the bleeding risk associated with anticoagulants either during dialysis or when administered to treat other medical conditions.

Percutaneous and surgical approaches for stroke prevention, as noted earlier in the discussion on atrial fibrillation, are also poorly studied in CKD patients. Calcified vessels may...
increase the risk of procedural complications, and clinical benefit has not been demonstrated for CKD populations.

**Emerging Diagnostic Tools and Therapies**

**Vascular Calcification**

Vascular calcification (Figure 6) is a strong risk factor for future CVD-related events in the general population and, notably, is an independent risk factor for CVD in CKD. Data from a post hoc analysis of 8 studies evaluating individuals in the general population receiving high-intensity statin therapy have recently suggested that statins may actually increase vascular calcification and in so doing may stabilize otherwise unstable plaques. Statins have not been conclusively shown to reduce CVD events in patients with ESRD; however, medial rather than intimal calcification predominates in patients with kidney disease. Medical calcification results from alterations in a number of factors unique to patients with kidney disease, namely changes in mineral metabolism and alterations in pathways linked to bone metabolism (see above). Routine clinical measures of vascular calcification cannot distinguish intimal from medial calcification. However, because patients with CKD and ESRD are at particularly high risk for medial calcification, calcification in general remains a potentially strong surrogate and an important potential therapeutic target to modify CVD in those with kidney disease.

**Albuminuria**

Although reduced eGFR is strongly associated with adverse outcomes, the risk of future cardiovascular events and mortality is better correlated with albuminuria than with eGFR. Most of these studies have assessed the severity of albuminuria using quantitative measures (eg, urinary albumin-to-creatinine or protein-to-creatinine ratio). However, semiquantitative measures such as urine dipstick assessment of albuminuria are also useful for risk stratification at all levels of baseline eGFR. A population-based study of >1 million people from Alberta, Canada, demonstrated that albuminuria was associated with marked increases in the risks of kidney failure, cardiovascular events, and all-cause mortality independently of eGFR (Figure 1). Other studies have shown that albuminuria is independently associated with the risk of stroke, myocardial infarction, and coronary revascularization procedures. These findings have been shown to apply to a broad range of populations, regardless of age, sex, ethnicity, and underlying risk factor profile, and extend to very low levels of albuminuria that were previously considered innocuous (15–29 mg/d). Collectively, these studies confirm that albuminuria is a powerful predictor of future cardiovascular events independently of eGFR, hypertension, diabetes mellitus, and traditional cardiovascular risk factors.

Although albuminuria is an unequivocal risk factor for CVD in CKD, it may not be an appropriate surrogate for CKD-related outcomes, and it is even possible certain therapies that improve CKD-related outcomes may in fact increase albuminuria.

**Carbamylated Albumin**

C-Alb responds to changes in dialysis dose, and unlike standard clinical measures of uremia (ie, blood urea, creatinine, urea reduction ratio, or Kt/V), C-Alb is strongly associated with mortality. As rapid assays for measurement of C-Alb become available, C-Alb may emerge as a useful marker to assess the efficacy of dialysis and adequacy of nutrition. C-Alb may also be considered when making treatment decisions on which patients are best treated with standard intermittent hemodialysis, ascertaining which patients require extended duration or increased frequency hemodialysis, and identifying patients with residual renal function who may be able to be adequately maintained on less frequent twice-weekly hemodialysis. Analogous to hemoglobin A1c, C-Alb measurement may also play a central role in testing the pharmacodynamic efficacy of these combined treatments and the need for supplemental nutritional measures.

**Frequent Hemodialysis**

Home hemodialysis use has increased, resulting in more patients with ESRD receiving nocturnal dialysis 6 times a week instead of intermittent hemodialysis 3 times a week. In small studies, intensification of dialysis frequency has been associated with a reduction in hypertension and an improvement in left ventricular mass. Interestingly, however, a follow-up study of patients originally assigned to frequent nocturnal hemodialysis does not support lower future mortality rates. Additional studies with specific markers that monitor uremic burden (eg, C-Alb) may be needed to better assess which ESRD patients may benefit from intensification of their dialysis regimen.
Health Services and Health Policy Changes

Health Policy Priorities for LMICs

Available data clearly show that the most rapid increases in noncommunicable chronic disease (NCD) prevalence will occur in LMICs.61,227,228 For example, during the last 3 decades, the prevalence of type 2 diabetes mellitus has increased nearly 5-fold in East Asia and South Asia compared with a doubling in the United States.56,61 Given that diabetes mellitus and hypertension cause both CKD and CVD, it seems clear that the prevalence of these 4 conditions will increase in parallel. This is especially the case in LMICs, where CKD and CVD may be more likely to remain undetected until later stages of illness.

Not surprisingly, awareness, treatment, and adequate control of CKD (alone or in combination with CVD) are low in LMICs, with the biggest gaps observed in the poorest patients.229 Lessons learned from the battle against tuberculosis, for which complex treatment regimens have been delivered in fixed-dose combinations by successful adoption of care pathways, can perhaps be used to tackle the growing burden of NCDs. Care pathways are structured protocols in which criteria-based medication prescription adjustment is the default approach to clinical encounters rather than the status quo, in which medication adjustments require deliberate action by the clinician. Although incompletely studied, care pathways may help to address quality gaps in NCD care.230

Data from RCTs indicate that prescribing fixed-dose combinations of cardioprotective medications (otherwise known as the polypill) can improve adherence rates compared with prescriptions for multiple tablets.231 Such combination treatments appear highly cost-effective232 and are potentially cost saving.233 Moreover, because the decision to prescribe the polypill is binary (rather than multifaceted, as when multiple medications are prescribed), wider use of the polypill may increase the likelihood that patients with NCDs would receive all recommended treatments, although this remains to be shown.

These collective observations suggest that care pathways and the polypill will be important tools for NCD control in LMICs.

Health Services and Health Policy Challenges for Developed Countries

Two interrelated challenges confront developed countries seeking to improve the quality of NCD care generally and the care of people with CKD and CVD specifically. First, the prevalence of people who have both CKD and CVD is not compatible with a specialist-based care model. Second, the health systems of wealthy countries are best equipped to deal with 1 disease at a time, but coexistent CKD and CVD can interact with each other (and with other comorbid conditions) to affect prognosis, function, communication between physicians, and the likelihood that treatment will be helpful or harmful. These 2 challenges imply the need to restructure health services for NCD care in most developed countries.

First, a more integrated approach to management is needed. Most patients with both CKD and CVD require relatively generic treatment that includes blood pressure control, interruption of the renin-angiotensin system, control of blood sugar, consideration of statin and aspirin, and advice on healthy weight, exercise, and smoking cessation. Arguably, only those with nephrotic-range proteinuria, very low eGFR (eg, <30 mL·min⁻¹·1.73 m⁻²), and evidence of collagen vascular disease or vasculitis would require involvement of a nephrologist per se, whereas only those with severe heart failure or valvular heart disease, symptoms suggesting the need for revascularization, or evidence of serious arrhythmia would require that a cardiologist be involved. In short, most patients with both CKD and CVD in developed countries might need to see just a single specialist. This approach would require agreement on the common elements of care and possibly changes to physician reimbursement structures. However, if successfully implemented, this strategy would increase the capacity to streamline care by eliminating unnecessary specialist visits.

Second, even 1 visit to a specialist may be unnecessary for many patients with NCDs. Strengthening the capacity for primary care practices to manage CKD, CVD, and other NCDs will be critical. Nonphysicians such as specially trained nurses could play an important role, using care pathways and other protocols230,234 that identify patients with “red flag” symptoms (eg, ongoing angina), signs (eg, severe edema), or laboratory results (eg, nephrotic range albuminuria, very low ejection fraction) who require prompt physician assessment. The majority of patients without such red flags could be cared for by the nurses, with or without input from allied health professionals such as dieticians or pharmacists.4,235,236 These models could allow teams led by a single physician to care for hundreds of patients with NCDs.

Other prerequisites for improving the care of people with CKD, CVD, and other NCDs in wealthy countries include comprehensively addressing the social determinants of health; engaging, educating, and empowering patients and the general public about the significance of effective self-management; and implementing a robust public health response to combat obesity, diabetes mellitus, and hypertension.

Summary

CVD is a leading cause of death among patients with CKD. Besides the traditional risk factors that contribute to both conditions, uremic toxins may be directly responsible for the pathogenesis of CVD in CKD. Both clinical and benchtop researchers will need to actively collaborate to characterize novel pathways and to identify new therapeutic targets to control this growing epidemic. There is an urgent need to continue performing well-designed clinical trials in the CKD and ESRD populations that target both traditional and nontraditional risk factors and not to assume that results of trials (positive or negative) done in the general population are applicable to individuals with kidney disease.

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Disclosures

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In the article by Tonelli et al, “Epidemiology and Mechanisms of Uremia-Related Cardiovascular Disease,” which published in the February 2, 2016, issue of the journal (Circulation. 2016;133:518–536), an error appeared in Figure 1C. The curve for stage 5 was labeled incorrectly as “mildly reduced” instead of “kidney failure”. The authors apologize for this error.

This correction has been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/133/5/518.full.

Figure. Relationships between cardiac events and loss of life expectancy resulting from cardiovascular disease (CVD) by stage of chronic kidney disease (CKD). A and B. The adjusted relative rate of all-cause mortality (ACM) and acute myocardial infarction as a function of glomerular filtration rate (eGFR; mL·min−1·1.73 m−2) and severity of albuminuria as assessed by albumin-to-creatinine ratio (ACR; normal, ACR <30 mg/g; mild, ACR 30–300 mg/g; or heavy, ACR >300 mg/g). C and D. Adjusted loss of life expectancy resulting from CVD by CKD stage. Loss is compared with life expectancy in people with normal or mildly impaired kidney function (stage 1–2, eGFR ≥60 mL·min−1·1.73 m−2) and normal or mildly increased albuminuria (stage 1, ACR <30 mg/g). RRT indicates renal replacement therapy. C and D are reproduced from The Lancet, Gansevoort et al7 with permission from the publisher. Copyright © 2013, Elsevier.