CORE CURRICULUM IN NEPHROLOGY

Cardiovascular Disease and CKD: Core Curriculum 2010

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Patients with CKD not only have a high prevalence of traditional CVD risk factors, but also are exposed to other nontraditional uremia-related CVD risk factors. In this Core Curriculum, we describe the epidemiologic characteristics and pathophysiologic process of CVD in patients with CKD and focus on several CVD risk factors. We then discuss manifestations and presentations of CVD in patients with CKD and review diagnostic and therapeutic options. As described next, many recommendations in CKD are based on extrapolation of data from the general population. However, we emphasize several of the important published trials on CVD in CKD (Tables 1 and 2). We do not focus on CVD in kidney transplant recipients.

EPIDEMIOLOGIC CHARACTERISTICS

Dialysis (CKD stage 5D)

- CVD is the leading cause of mortality, accounting for nearly 45% of deaths at all ages; the high mortality is due to both a high prevalence of CVD and a high case fatality rate in those with heart failure or acute myocardial infarction
- Of all deaths, 25%-30% (50%-60% of cardiovascular deaths) are classified as cardiac arrest/cause unknown or arrhythmia
- There are conflicting data about whether peritoneal dialysis or hemodialysis patients are at higher risk of CVD
  - Results of studies vary depending on the study population, statistical method used to adjust for case mix, country where the study is performed, incident versus prevalent patients, and dialysis vintage
- Observational studies suggest that daily dialysis and nocturnal hemodialysis may be associated with improved blood pressure control, decreased left ventricular hypertrophy (LVH), and better control of mineral metabolism abnormalities
  - In a small randomized controlled trial (n = 52), frequent nocturnal dialysis was associated with improved left ventricular mass (using cardiovascular magnetic resonance imaging) in comparison to standard of care
- The Frequent Hemodialysis Network has 2 ongoing parallel randomized trials
  - Both studies have 2 primary outcomes
    - Composite of mortality with change in the 36-Item Short Form Health Survey (SF-36) RAND physical health composite
    - Change in left ventricular mass
  - Daily trial: 250 patients will be randomly assigned to either conventional hemodialysis 3 days per week or frequent hemodialysis 6 days per week
  - Nocturnal trial: 150 patients will be randomly assigned to either conventional home hemodialysis 3 days per week or nocturnal home hemodialysis 6 times per week

CKD Stages 3-4

- High prevalence of CVD in incident dialysis patients suggests that CVD develops before the onset of kidney failure
- Higher prevalence of coronary artery disease (CAD), heart failure, and CVD risk factors than in the general population
- Graded and independent relationship between estimated glomerular filtration rate (GFR) and CVD outcomes, particularly in individuals with estimated GFR <45 mL/min/1.73 m^2 (<0.75 mL/s/1.73 m^2; Fig 1)

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Originally published online as doi:10.1053/j.ajkd.2010.03.019 on July 5, 2010.
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0272-6386/10/5602-0021$36.00/0
doi:10.1053/j.ajkd.2010.03.019

Table 1. Selected Randomized Clinical Trials in Dialysis Patients With Focus on Clinical CVD Outcomes/Mortality

Intervention	Trial Name	Population	N	Primary Outcome[a]	Result[b]	Comments
			Completed Trials			
High vs standard dose; high- vs low-flux membrane	HEMO	HD	1,846	All-cause mortality	−	
High- vs low-flux membrane	MPO	Incident HD	738	All-cause mortality	−	Benefit in those with albumin ≤4 g/dL
Carvedilol vs placebo		HD & dilated cardiomyopathy	114	Change in LVEDV, LVESV, EF, clinical status	+	Decreased morbidity & mortality
Amlodipine vs placebo		HD & hypertension	251	All-cause mortality	−	Beneficial effect on CVD outcomes
Candesartan vs placebo		HD & no CVD	80	Composite CVD	+	
Fosinopril vs placebo	FOSIDIAL	HD & LVH	397	Composite CVD	−	
N-Acteylcysteine vs placebo		HD	134	Composite CVD	+	
Vitamin E vs placebo	SPACE	HD & prevalent CVD	196	Composite CVD	+	
Atorvastatin vs placebo	4D	HD & diabetes	1,255	Composite CVD	−	
Rosuvastatin vs placebo	AURORA	HD	2,776	Composite CVD	−	
Folic acid + pyridoxine + cyanocobalamin vs placebo	HOST	HD or PD & hyperhomocysteinemia	751	All-cause mortality	−	
Folic acid, 15 vs 5 vs 1 mg		HD or PD	510	Composite CVD	−	
Sevelamer vs calcium-containing phosphate binders	DCOR	HD + phosphate-binder therapy	2,103	All-cause mortality	−	
Epoetin to target Hct of 42% vs 30%		HD & HF or IHD	1,233	Composite CVD	−	Trend toward worse outcomes in higher HCT group
			Ongoing Trials			
Cinacalcet vs placebo	EVOLVE	HD & PTH ≥300 pg/mL	3,883	Composite CVD	NA	
Simvastatin + ezetimibe vs placebo	SHARP	HD component of SHARP	6,000	Composite CVD	NA	
Growth hormone vs placebo	OPPORTUNITY	HD & hypoalbuminemia	2,500	All-cause mortality	NA	

Abbreviations: AURORA, Assessment of Survival and Cardiovascular Events; CVD, cardiovascular disease; 4D, Die Deutsche Diabetes Dialyse Studie; DCOR, Dialysis Clinical Outcomes Revisited; EF, ejection fraction; EVOLVE, Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events; FOSIDIAL, Fosinopril in Dialysis Study; Hct, hematocrit; HD, hemodialysis; HEMO, Hemodialysis Study; HF, heart failure; HOST, Homocysteinemia in Kidney and Endstage Renal Disease; IHD, ischemic heart disease; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; MPO, Membrane Permeability Outcome; NA, not available; PD, peritoneal dialysis; PTH, parathyroid hormone; SHARP, Study of Heart and Renal Protection; SPACE, Secondary Prevention With Antioxidants of Cardiovascular Disease in Endstage Renal Disease.

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[a]Composite CVD outcome may include all-cause mortality, and each trial may have different cardiovascular events.

[b]Results reported are for primary outcome of the study: + indicates benefit of intervention, − indicates no significant benefit.

Table 2. Selected Randomized Clinical Trials in Patients with CKD Stages 1-4 With Focus on Clinical CVD Outcomes/Mortality

Intervention	Trial Name	Population	N	Primary Outcome[a]	Result[b]	Comment
			Completed Trials			
Fosinopril vs placebo; pravastatin vs placebo	PREVEND IT	Microalbuminuria	864	Composite CVD	−	Trend to decrease in CVD events in fosinopril group
Epoetin alfa to target Hb of 13.5 vs 11.3 g/dL	CHOIR	CKD, GFR of 15-50 mL/min/1.73 m^2, Hb <11 g/dL	1,432	Composite CVD	Increased risk of primary outcome in higher Hb group	
Epoetin beta to target Hb of 13-15 vs 10.5-11.5 g/dL	CREATE	GFR of 15-35 mL/min/1.73 m^2, Hb of 11-12.5 g/dL	603	Composite CVD	−	
Darbepoetin alfa vs placebo	TREAT	DM, CKD, & anemia	4,038	Composite CVD	−	Increased risk of stroke in higher Hb group
Vitamin B_6 + B_9 + B_{12} vs placebo	HOST	CKD stage 4 & hyperhomocysteinemia	1,305	All-cause mortality	−	
			Ongoing Trials			
Simvastatin + ezetimibe vs placebo	SHARP	CKD component of SHARP	3,000	Composite CVD	NA	
ACEi + ARB vs ACEi vs ARB	LIRICO	Micro-/macroalbuminuria	2,100	Composite CVD & kidney outcomes	NA	
SBP <120 vs SBP <140 mm Hg	SPRINT	CKD component of SPRINT (GFR of 30-59 mL/min/1.73 m^2)	(~3,000 with CKD)	Composite CVD	NA	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CHOIR, Correction of Hemoglobin Outcomes in Renal Insufficiency; CKD, chronic kidney disease; CREATE, Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; Hb, hemoglobin; HOST, Homocysteinemia in Kidney and Endstage Renal Disease; LIRICO, Long-term Impact of RAS Inhibition on Cardiorenal Outcomes; NA, not available; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; SBP, systolic blood pressure; SHARP, Study of Heart and Renal Protection; SPRINT, Systolic Blood Pressure Intervention Trial; TREAT, Trial to Reduce Cardiovascular Events With Aranesp Therapy.

Reference not included in other parts of this article:

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[a]Composite CVD outcome may include all-cause mortality, and each trial may have different cardiovascular events.

[b]Results reported are for primary outcome of the study. + indicates benefit of intervention, − indicates no significant benefit.

CKD Stages 1-2

- Independent association between microalbuminuria and clinical CVD in cross-sectional analysis
- Higher prevalence of surrogates of CVD in those with microalbuminuria, such as
  - LVH in patients with hypertension
  - Carotid arterial intima-media thickening in patients with diabetes

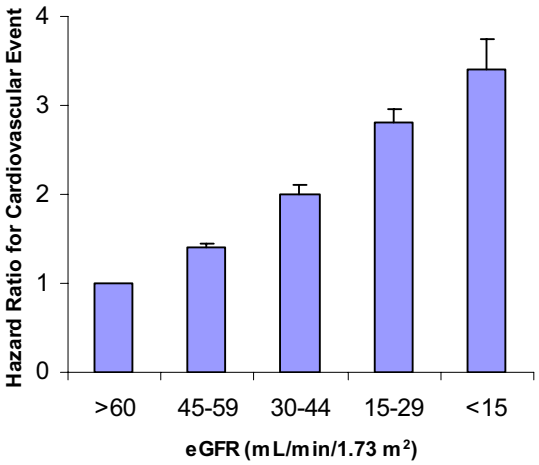

Figure 1. Hazard ratios for cardiovascular events according to baseline estimated glomerular filtration rate (eGFR), adjusted for baseline age, sex, income, education, coronary disease, chronic heart failure, stroke or transient ischemic attack, peripheral artery disease, diabetes, hypertension, dyslipidemia, cancer, hypoalbuminemia, dementia, liver disease, proteinuria, prior hospitalizations, and subsequent dialysis requirement. Plotted using data from Go et al (*N Engl J Med.* 2004;351(13):1296-1305).

    - Brain white matter hyperintensity volume in older adults
- Microalbuminuria is independently associated with CVD outcomes and all-cause mortality in those with and without diabetes
- Albuminuria, even with albumin excretion less than the microalbuminuria range, is associated independently with CVD outcomes; no threshold has been defined, and in some studies, the risk extends to <10 μg/mg
- Microalbuminuria may represent kidney disease itself or be a manifestation of systemic endothelial disease burden
- In PREVEND IT (Prevention of Renal and Vascular End Stage Disease Intervention Trial), treatment with angiotensin-converting enzyme (ACE) inhibitors in patients with microalbuminuria showed a trend to reducing CVD outcomes

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PATHOPHYSIOLOGIC PROCESS

There are 3 primary forms of CVD in patients with CKD: atherosclerosis, arteriosclerosis, and cardiomyopathy. Each of the risk factors described next may predispose to one form of CVD in particular or combinations thereof.

Classification of Arterial Disease

Atherosclerosis

- Occlusive disease of the vasculature
- Focal process of plaque formation resulting in luminal narrowing
- Manifestation of risk factors that are prevalent as kidney disease progresses, including a highly atherogenic lipid profile

Arteriosclerosis

- Nonocclusive remodeling of the vasculature
- Characterized by diffuse dilatation and hypertrophy of large arteries with loss of arterial elasticity and reduced arterial compliance
- Risk factors include volume overload and mineral metabolism abnormalities
- Manifestations of arteriosclerosis include
  - LVH
  - Decreased coronary perfusion
  - Increased systolic blood pressure and pulse pressure

Cardiomyopathy

LVH resulting from either pressure or volume overload reflects appropriate adaptation by the heart to these forces. As workload increases over time, increased oxygen demands by the hypertrophied left ventricle ultimately may exceed its perfusion, resulting in ischemia and eventual myocyte death. The end stage of this process is cardiomyopathy.

Pressure Overload

- Leads to concentric thickening of the left ventricular wall to allow for generation of greater intraventricular pressure from
  - Increased cardiac afterload from hypertension and aortic stenosis
  - Reduced arterial compliance from arteriosclerosis

Volume Overload

- Leads to eccentric hypertrophy secondary to the addition of new sarcomeres in series and may be related to
  - Anemia
  - Increased extracellular volume
  - Arteriovenous fistula with high blood flow

Initial physiology often is consistent with diastolic dysfunction, but as this process progresses, myocardial fibrosis may ensue, and with sustained maladaptive forces, dilated cardiomyopathy may develop.

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Box 1. Traditional and Nontraditional Cardiovascular Risk Factors

Traditional Risk Factors	Nontraditional Factors
• Older age • Male sex • Hypertension • Higher LDL cholesterol • Lower HDL cholesterol • Diabetes • Smoking • Physical inactivity • Menopause • Family history of coronary disease • Left ventricular hypertrophy • White race	*Factors particular to individuals with kidney disease* • Anemia • Volume overload • Abnormal mineral metabolism • Electrolyte imbalances • Albuminuria *Factors in the general population* • Lipoprotein(a) and Apo(a) isoforms & lipoprotein remnants • Homocysteine • Oxidative stress/inflammation • Malnutrition • Thrombogenic factors • Sleep disturbances • High sympathetic tone • Altered nitric oxide/endothelin balance

Abbreviations: Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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OVERVIEW OF RISK FACTORS

CVD risk factors are defined as characteristics, both modifiable and nonmodifiable, that increase the risk of developing CVD.

Traditional CVD Risk Factors

The risk factors shown in the left-hand side of Box 1 were defined in the Framingham Heart Study.

- Many traditional risk factors, such as diabetes and hypertension, are more prevalent in patients with CKD than in the general population
- The Framingham coronary risk equation severely underestimates CVD risk in dialysis patients
- Individuals with CKD stages 3-4 have higher coronary risk scores using the Framingham prediction equations compared with the general population; however, with poor discrimination and calibration reflecting:

- Greater severity of traditional CVD risk factors
- Role of nontraditional risk factors

Nontraditional Risk Factors

The right-hand side of Box 1 shows putative CVD risk factors that increase in prevalence as kidney function decreases, but were not described in the original Framingham Heart Study.

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CVD RISK FACTORS: HYPERTENSION AND BLOOD PRESSURE

Hypertension is both a cause and a result of kidney disease. Of patients with CKD stages 1-4, a total of 70%-80% have hypertension and the prevalence increases as GFR decreases.

Dialysis

- High blood pressure is an independent risk factor for nonfatal CVD events
- There is a "U"-shaped relationship between blood pressure and all-cause and CVD mortality, with increased risk at both high and low blood pressures
- The relationship between baseline blood pressure and mortality changes over time, with low systolic blood pressure associated with increased mortality in the first 2 years and the adverse effects of high systolic blood pressure apparent after 3 years of dialysis therapy
- Increased pulse pressure, a marker of vascular stiffness, is associated with increased mortality in hemodialysis patients
- Intradialytic hypotension is a relatively common occurrence during hemodialysis

Box 2. Evidence Grades for KDOQI Guideline Recommendations

Grade A

It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.

Grade B

It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.

Grade C

It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes.

Abbreviation: KDOQI, Kidney Disease Outcomes Quality Initiative.

Reproduced by permission from National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. *Am J Kidney Dis.* 2005;45(suppl 3):S1-154.

  - Represents inability of the heart or blood vessels to appropriately compensate for decreased blood volume
  - Heart failure itself in the absence of overt volume overload
- Intradialytic hypertension also may be associated with adverse outcomes
- Absence of clinical trials delineating target blood pressure in dialysis patients
- A meta-analysis of 8 randomized controlled trials of blood pressure–lowering medications showed that use of blood pressure–lowering medication was associated with lower risk of CVD events compared with controls; however, there was significant heterogeneity among studies

CKD Stages 3-4

- Increased systolic blood pressure is an independent risk factor for CVD outcomes in both diabetic and nondiabetic patients

KDOQI Guideline Recommendations

A summary of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) grading system for guideline recommendations is shown in Box 2.

- In dialysis patients, goal predialysis and postdialysis blood pressures are <140/90 and <130/80 mm Hg, respectively (level C evidence)
- ACE inhibitors or angiotensin II receptor blockers (ARBs) should be preferred in patients on dialysis (level C evidence)
- In patients with CKD stages 1-4, goal blood pressure is <130/80 mm Hg for prevention of CVD and kidney disease progression (level B evidence)
- Dietary sodium intake <2.4 g/d should be recommended in most adults with CKD and hypertension (level A evidence)
- Use of ACE inhibitors or ARBs in patients with CKD stages 1-4 as preferred agents in those with either diabetes mellitus or urine protein-creatinine ratio >200 mg/g in a spot urine specimen (level A evidence)

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CVD RISK FACTORS: DYSLIPIDEMIA

Although the nature of dyslipidemia can be highly variable, it is common in all stages of CKD.

Dialysis

- In hemodialysis patients, high-density lipoprotein (HDL) cholesterol typically is low, low-density lipoprotein (LDL) cholesterol level is normal to low, and triglyceride, lipoprotein(a), and atherogenic oxidized LDL cholesterol levels are high compared with the general population
- Peritoneal dialysis patients tend to have lower HDL cholesterol and higher triglyceride, LDL cholesterol, and apolipoprotein levels than hemodialysis patients; may be due to
  - Absorption of glucose from the peritoneal dialysis fluid, which provides a substrate for increased lipoprotein synthesis
  - Hypoalbuminemia secondary to peritoneal protein losses leading to overproduction of LDL cholesterol
  - Loss of HDL across the peritoneum
- Lower total cholesterol levels are associated with higher mortality, possibly because low cholesterol level is a surrogate for malnutrition and inflammation
- Higher total cholesterol levels are associated with increased CVD risk in patients with preserved nutritional status
- Two recent randomized controlled trials have been published about the effect of lipid-lowering therapy on CVD events in hemodialysis patients
  - In the 4D Study (Die Deutsche Diabetes Dialyse Studie), although atorvastatin decreased LDL cholesterol levels, it did not decrease the primary composite CVD outcome in patients with type 2 diabetes
  - Similarly, in the AURORA (Assessment of Survival and Cardiovascular Events) Study, rosuvastatin decreased LDL cholesterol levels, but had no significant effect

on the composite primary end point of death from CVD causes, nonfatal myocardial infarction, or nonfatal stroke compared with placebo

CKD Stages 3-4

- Higher prevalence of increased LDL cholesterol and triglyceride and low HDL cholesterol levels compared with the general population
- Nephrotic-range proteinuria can exacerbate dyslipidemia
- Post hoc analyses of secondary prevention trials of statins in the general population show similar benefits in patients with and without CKD
  - In the CARE (Cholesterol and Recurrent Events) Study, participants with decreased GFR (creatinine clearance <75 mL/min [<1.25 mL/s]) receiving pravastatin had a lower incidence of death from coronary disease or symptomatic nonfatal myocardial infarction than those receiving placebo
  - In a pooled analysis using data from 3 randomized trials, pravastatin decreased CVD events compared with placebo in patients with CKD
- In a meta-analysis of secondary prevention of CVD, statins significantly decreased lipid concentrations and CVD end points in patients with CKD, but had no benefit on all-cause mortality
- In a primary prevention study, atorvastatin decreased CVD events, but not all-cause mortality, in a post hoc analysis of the CKD subgroup of CARDS (Collaborative Atorvastatin Diabetes Study)

KDOQI Guideline Recommendations

- All patients with CKD, even in the absence of known CVD, should be considered at high risk of CVD outcomes
- Goal lipid levels are LDL cholesterol <100 mg/dL (<2.59 mmol/L) and non-HDL cholesterol <130 mg/dL (<3.36 mmol/L) (level B evidence)

Additional Considerations

- The KDOQI guidelines potentially are still valid for CKD stage 3, but likely do not apply to dialysis patients, given results of the 4D Study and AURORA, particularly in individuals with an expected remaining lifespan less than 5 years
- SHARP (Study of Heart and Renal Protection), a randomized trial of a combination of simvastatin and ezetimibe, will offer additional guidance in individuals with CKD stages 4-5

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CVD RISK FACTORS: DIABETES MELLITUS

Diabetes is the leading cause of kidney failure in the United States. Approximately 53% of incident dialysis patients in the United States have diabetes.

Dialysis

- Diabetes is an independent risk factor for ischemic heart disease, heart failure, and all-cause mortality
- Worse long-term outcomes after coronary interventions than nondiabetic patients
- Lack of studies of the relationship between glycemic control and CVD outcomes

- Currently, there are no evidence-based recommendations from KDOQI or KDIGO (Kidney Disease: Improving Global Outcomes) regarding diabetes management

CKD Stages 3-4

- Leading causes of kidney disease with microalbuminuria as the first clinical manifestation of diabetic nephropathy
- Risk factor for CVD events and all-cause mortality
- Treatments that decrease urinary albumin excretion may slow the progression of kidney disease and also decrease CVD outcomes

KDOQI Guideline Recommendations

- Adoption of healthy lifestyle practices
- Body mass index should be within the normal range (level C evidence)
- Hypertensive patients with diabetes and CKD stages 1-4 should be treated with ACE inhibitors or an ARB, usually in combination with a diuretic (level A evidence)
- Target LDL cholesterol level in people with diabetes and CKD stages 1-4 should be $<$100 mg/dL ($<$2.59 mmol/L); $<$70 mg/dL ($<$1.81 mmol/L) is a therapeutic option (level B evidence)
- LDL cholesterol level $>$100 mg/dL ($>$2.59 mmol/L) should be treated with a statin (level B evidence)
- Target hemoglobin A_{1c} level $<$7.0% for patients with CKD stages 3-4 (level A evidence)
- Normotensive patients with diabetes and macroalbuminuria should be treated with an ACE inhibitor or ARB (level C evidence)
- In normotensive patients with diabetes and microalbuminuria, treatment with an ACE inhibitor or ARB may be considered (level C evidence)

Additional Considerations

- Recent studies of the general population have questioned whether tight glucose control in patients with type 2 diabetes carries some risk
- In elderly patients with diabetes and CKD, targeting tight glucose control remains controversial and some have recommended higher target hemoglobin A_{1c} levels (8%-8.5%)

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CVD RISK FACTORS: LVH

LVH represents a physiologic adaptation to a long-term increase in myocardial work requirements. It can be considered as both a traditional risk factor and a CVD outcome.

Dialysis

- LVH is an independent risk factor for adverse CVD outcomes
- Assessed using echocardiography, 75%-80% of incident dialysis patients have LVH
- LVH also is seen in children requiring hemodialysis when there typically is an absence of ischemic heart disease

CKD Stages 3-4

- Prevalence of LVH increases as GFR decreases; approximately 30% and 45% of patients with CKD stages 3 and 4 have LVH, respectively

Clinical Sequelae

- Myocardial infarction
- Intradialytic hypotension
- Angina
- Heart failure
- Sudden cardiac death

Diagnosis

- Established using echocardiography
  - Screening echocardiography currently recommended for incident dialysis patients when patients have achieved dry weight (ideally within 1-3 months of dialysis therapy initiation) (level A evidence) and 3-year intervals thereafter (level B evidence)
  - Best assessed on an interdialytic day because both significant volume depletion and overload decrease left ventricular inotropy
- Magnetic resonance imaging is more sensitive for assessing left ventricular mass, but is not yet widely available and is more expensive
  - Magnetic resonance imaging with gadolinium is contraindicated in patients with estimated GFR <30 mL/min/1.73 m^2 (<0.50 mL/s/1.73 m^2), including patients on dialysis therapy, given the risk of nephrogenic systemic fibrosis

Treatment

- Goal is afterload reduction, blood pressure control, and volume management
- In dialysis patients, blood pressure control through achievement of dry weight is the mainstay of treatment
  - Blood pressure agents are added if blood pressure remains high despite this intervention
  - ACE inhibitors and ARBs may confer additive cardioprotective benefit independent of blood pressure lowering
- In patients with CKD stages 1-4, mainstay of treatment is similar to the general population and includes ACE inhibitors, ARBs, diuretics, β-blockers, and calcium channel blockers
  - Challenges include more frequent hyperkalemia with blockade of the renin-angiotensin-aldosterone system

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CVD RISK FACTORS: SMOKING

- Few studies have examined specific effects of smoking in dialysis patients
- Evaluation of US Renal Data System (USRDS) data showed that smoking was a strong independent risk factor for incident heart failure, incident peripheral vascular disease, and all-cause mortality
- Given marked benefits of smoking cessation in the general population, the general consensus is to recommend smoking cessation

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CVD RISK FACTORS: ANEMIA

Anemia is highly prevalent in patients with CKD, primarily, but not exclusively, due to erythropoietin deficiency, erythropoietin hyporesponsiveness, and iron deficiency.

Dialysis

- In observational studies, anemia is associated with eccentric LVH, ventricular dilatation, development of de novo heart failure, and mortality
- In the Normal Hematocrit Trial, targeting a hematocrit of 42% compared with 30% in those with ischemic heart disease or heart failure resulted in a trend toward worse CVD outcomes

CKD Stages 3-4

- In observational studies, anemia is associated with LVH and CVD events

- Three large randomized trials have been published on the effect of anemia treatment on CVD events
  - In the CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) Study, correction of anemia to a hemoglobin target of 13-15 g/dL (130-150 g/L) compared with correction to 10.5-11.5 g/dL (105-115 g/L) did not reduce the risk of the primary CVD composite
  - In the CHOIR (Correction of Hemoglobin Outcomes in Renal Insufficiency) Study, targeting a hemoglobin level of 13.5 g/dL (135 g/L) compared with 11.3 g/dL (113 g/L) was associated with increased risk of death and CVD hospitalizations and no incremental improvement in quality of life
  - In TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy), targeting a hemoglobin level of 13 g/dL (130 g/L) compared with rescue therapy with darbepoetin alfa when hemoglobin level was <9 g/dL (<90 g/L) did not reduce the risk of the 2 primary composite outcomes (either death or CVD event or death or kidney event) and was associated with increased risk of stroke

KDOQI Guideline Recommendations

- Selection of the hemoglobin target and level at which erythropoietin-stimulating agent therapy is initiated should be individualized based on consideration of potential benefits (improvement in quality of life and avoidance of transfusion) and potential harms (risk of life-threatening adverse events)
- Hemoglobin target generally should be in the range of 11.0-12.0 g/dL (110-120 g/L)
- Hemoglobin target should not be >13.0 g/dL (>130 g/L) (moderately strong evidence)

Additional Considerations

- Guidelines will need to be reassessed given results of TREAT

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CVD RISK FACTORS: OXIDANT STRESS AND INFLAMMATION

Background

- Proposed as a unifying concept linking both traditional and other nontraditional risk factors in CKD
- Imbalance between pro-oxidants and antioxidants (oxidant defenses) that leads to tissue damage
  - Factors that increase oxidant stress
    - Inflammation
    - Malnutrition (by decreasing antioxidant defenses)
    - Uremic toxins
    - Dialysis procedure
  - Factors that decrease antioxidants
    - Plasma protein-associated free thiols, such as glutathione

Dialysis

- Independent association between inflammation and risk of adverse CVD outcomes
- Two small randomized trials of dialysis patients suggest that decreasing oxidative stress may improve outcomes

- Vitamin E administration in patients with prevalent CVD was associated with lower incidence of primary composite CVD end point compared with placebo
- Acetylcysteine administration was associated with a decrease in composite CVD end points

- Because the trials were small, there currently is insufficient evidence to recommend screening or treatment of inflammation and oxidative stress

CKD Stages 3-4

- Inflammatory markers, including C-reactive protein, increased white blood cell count, and fibrinogen, are associated with adverse CVD outcomes
- No significant difference in magnitude of risk was associated with inflammatory markers in individuals with estimated GFR <60 and >60 mL/min/1.73 m^2 (<1 and >1 mL/s/1.73 m^2)

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CVD RISK FACTORS: HOMOCYSTEINE

- Until recently, homocysteine was implicated in the general population as a risk factor for myocardial infarction and stroke
- Levels increase as GFR decreases
- Trials have shown that treatment with high doses of B vitamins decreases homocysteine levels, but do not decrease CVD outcomes in patients with CKD

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CVD RISK FACTORS: NITRIC OXIDE, ASYMMETRIC DIMETHYLARGININE (ADMA), AND ENDOTHELIAL FUNCTION

- In patients with CKD, decreased nitric oxide production likely reflects
  - Substrate (L-arginine) limitation
  - Increased levels of ADMA, which is an endogenous inhibitor of nitric oxide synthase
- In CKD, particularly in states of high oxidative stress
  - ADMA level increases as GFR decreases
  - ADMA is associated with a more rapid decrease in kidney function and increased CVD risk and all-cause mortality
- Pharmacologic interventions aimed at decreasing plasma ADMA levels have shown inconsistent results

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CVD RISK FACTORS: CKD–MINERAL BONE DISORDER

- Mechanisms linking abnormal mineral metabolism with vascular calcification and arteriosclerosis are complex and not fully understood
  - Reflects interrelationship among hyperphosphatemia, secondary hyperparathyroidism, vitamin D deficiency, and other promoters or inhibitors of calcification
  - Active cellular process in which vascular smooth muscle cells differentiate into osteoblast-like cells, which are able to synthesize proteins that favor vascular calcification

- Abnormalities in mineral metabolism also may promote cardiomyopathy
- Arterial calcification, specifically medial calcification, is more common in individuals with CKD
- Independent associations between coronary and peripheral arterial calcification with mortality
- Use of non–calcium-containing phosphorus binders has been associated with decreased vascular calcification in some, but not all, studies of CKD stages 3-5
- Higher serum phosphate levels, lower 25 hydroxyvitamin D levels, and lower use of 1,25 dihydroxyvitamin D (or analogues) are associated with increased CVD events in observational studies
- No trial data to show a benefit for clinical CVD outcomes or mortality for any of the listed interventions in any stage of CKD

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CVD SYNDROMES: ISCHEMIC HEART DISEASE

Epidemiologic Characteristics

- Ischemic heart disease is prevalent in all stages of CKD
- Approximately 40% of incident dialysis patients have coronary heart disease

Diagnosis

Routine screening currently is not recommended in the absence of clinical manifestations or being on a transplant list.

Laboratory Tests

- Markers similar to those used in the general population
  - Creatine kinase
  - Myocardial creatine kinase (MB isoform)
  - Myoglobin
  - Natriuretic peptides
  - Troponin I and T
    - Diagnosis of acute myocardial infarction accomplished best by following the trend of either troponin I or T and other cardiac injury markers
    - Troponin T more than troponin I level frequently is increased in asymptomatic dialysis patients
    - Increased troponin T level in asymptomatic dialysis patients may indicate subclinical myocardial injury, LVH, or cardiomyopathy and is associated with adverse short- and long-term outcomes
    - Interpretation of the prognostic potential of troponins (both I and T) may change with the development of more sensitive assays

Electrocardiogram

- High prevalence of baseline electrocardiogram (ECG) abnormalities
- Exercise stress electrocardiography is limited because of baseline ECG abnormalities and inability to achieve adequate heart rate in response to exercise

Cardiac Imaging

- Echocardiography at rest for evaluation of cardiac structure and function
- Pharmacologic nuclear or echocardiographic stress tests are useful, and detection of perfusion defects and structural abnormalities are associated with long-term outcomes
- Electron beam computed tomography is a sensitive method to detect vascular calcification; however, it may not be ideal in patients with CKD because it is unable to distinguish between intimal calcifications of atheroscle-

rosis and medial calcification that is common in CKD

Cardiac Catheterization

- Anatomic description and possible repair of the coronary anatomy
- In dialysis patients who are at high risk of CAD, coronary angiography may be appropriate, even when stress imaging test results are negative due to lower diagnostic accuracy of noninvasive stress imaging tests (level C evidence)
- Conversely, patients may have ischemic heart disease in the absence of large-vessel coronary disease
- Higher risk population for complications, including bleeding and re-stenosis with or without stent placement
  - Recent study showed that approximately 22% of dialysis patients who underwent percutaneous coronary intervention received a contraindicated antithrombotic (low-molecular-weight heparin and eptifibatide), which in turn was associated with increased risk of in-hospital major bleeding and mortality
- Preservation of existing kidney function is an important consideration in all stages of kidney disease
- The incidence of significant contrast-induced nephropathy can be decreased with careful management and conservative use of iodinated contrast

Treatment

- No large randomized clinical trial has focused exclusively on patients with CKD.
- Many studies have excluded participants with increased serum creatinine levels
- Post hoc subgroup analyses derived from larger clinical trials showed benefits in patients with CKD stages 3-4 similar to those in the general population; treatment strategies for the most part therefore mirror those in the general population

Acute Coronary Syndrome

- Treatment similar to that in the general population
- Patients with ST-segment elevation myocardial infarction should receive acute reperfusion therapy
- In dialysis patients, the potential for increased hemorrhagic risk is associated with thrombolytic therapy, and percutaneous coronary intervention is the preferred treatment if it is available (level C evidence)
- Specific attention should be given to medications that have altered clearance in patients with CKD (eg, low-molecular-weight heparin)

Chronic Ischemic Heart Disease

- Few trial data for secondary prevention strategies that have focused on patients with CKD
- Medical management of chronic CAD similar to that in the general population and should include aspirin, β-blockers, nitroglycerin, ACE inhibitors or ARBs, statins, and calcium channel blockers (level C evidence in dialysis)
- Challenges specific to the CKD population include
  - More frequent hyperkalemia with blockade of the renin-angiotensin-aldosterone system
  - Increased risk of rhabdomyolysis with dual statin and fibrate therapy (a combination that should be avoided in those with advanced CKD)
- In dialysis patients, predialysis blood pressure goal is $<$140/90 mm Hg while avoiding orthostatic and intradialytic hypotension (level C evidence)
  - As mentioned, achievement of dry weight is the mainstay of therapy and blood pressure agents are added if blood pressure remains high despite this intervention
- In patients with CKD stages 1-4, target blood pressure is $<$130/80 mm Hg
- Serum LDL cholesterol level $<$100 mg/dL ($<$2.59 mmol/L)
- Smoking cessation
- Observational studies suggest that patients with 3-vessel and/or left main disease do better with coronary artery bypass versus percutaneous interventions (level C evidence in dialysis); however, these studies are limited by selection bias

Primary Prevention

- Limited trial data on primary prevention strategies that have focused on patients with CKD
- Treatment strategies mirror those in the general population

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CVD SYNDROMES: HEART FAILURE

Heart failure is characterized by volume overload, pulmonary edema, and dyspnea. Heart failure may occur as a result of either left ventricular systolic dysfunction or diastolic dysfunction, in which the left ventricle has a normal ejection fraction, but impaired filling.

Epidemiologic Characteristics

- Heart failure is diagnosed in approximately 25% of hemodialysis and 18% of peritoneal dialysis patients annually, and approximately 55% of prevalent hemodialysis patients have a history of heart failure
- Those with CKD stages 3-4 have approximately twice the risk of hospitalization for incident heart failure and death compared with participants with estimated GFR >90 mL/min/1.73 m^2 (>1.50 mL/s/1.73 m^2) regardless of the presence of baseline coronary disease

Diagnosis

- Clinical diagnosis
- Chest x-ray
- Echocardiography
- BNP and pro-BNP
  - Both BNP and pro-BNP levels are increased in CKD
  - Pro-BNP is significantly cleared by the kidneys and thus more closely correlated with estimated GFR than BNP level
  - In the earlier stages of CKD, BNP and pro-BNP levels are useful for the diagnosis of acute heart failure; however, different cutoff values may be required
  - Both BNP and pro-BNP are associated with LVH, systolic dysfunction, CVD, and all-cause mortality in patients with CKD
  - BNP has not been shown to be useful as a measure of volume status in dialysis patients

Treatment

Short-term Management

- Dialysis: ultrafiltration is the mainstay of therapy
- CKD stages 3-4: diuretics are the mainstay of therapy

Long-term Management

- Limited data exist regarding CKD-specific long-term treatment of heart failure
- Post hoc analyses of clinical trials suggest that most interventions in the general population also apply
- β-Blocking agents beneficial with evidence supporting carvedilol use to decrease mortal-

ity risk in dialysis patients with dilated cardiomyopathy
- ARBs decrease the risk of developing heart failure in patients with diabetes and proteinuria in CKD stages 3-4
- Aldosterone blockers may be useful, although use may be limited by hyperkalemia, especially when used in conjunction with ACE inhibitors and/or ARBs
- Cardiac glycosides (eg, digoxin) decrease morbidity, but not mortality, in the general population
  - No specific studies of cardiac glycosides in CKD
  - Use extremely judiciously, with careful attention to dosage, drug levels, and potassium balance

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CVD SYNDROMES: PERICARDIAL DISEASE

Epidemiologic Characteristics

- Pericardial disease generally is associated with CKD stage 5

Types

Uremic Pericarditis

- Can occur before or within 8 weeks of initiation of dialysis therapy
- Pathogenesis is unclear, although there is correlation with degree of azotemia
- Rare, but remains an indication for and responds well to initiation of dialysis therapy

Dialysis-Associated Pericarditis

- Occurs after a patient is stabilized on dialysis therapy
- Precise cause is unknown, but may be related to inadequate dialysis and volume overload
- May be less frequent in the present era of increased dialysis dose

Clinical Sequelae

- Heart failure
- Hypotension

Diagnosis

- Nonspecific symptoms, such as chest pain, fever, chills, malaise, dyspnea, and cough
- Pericardial friction rub on physical examination
- When hemodynamically significant, pericardial effusion may be characterized by hypotension, particularly during the hemodialysis session
- Dialysis-related pericarditis often does not manifest with the classic ECG finding of diffuse ST-segment elevation
- On echocardiography, effusions may be absent in patients who have adhesive noneffusive pericarditis

Treatment

- Dependent on symptoms and effusion size
  - Small asymptomatic pericardial effusions can be commonly seen in dialysis patients and require no acute intervention
  - Large effusions
    - Present a risk for tamponade
    - Mainstay of therapy is intensification of hemodialysis therapy, but effective only approximately 50% of the time
    - Heparin therapy avoided during dialysis out of concern for hemorrhagic tamponade
    - Adjuvant medical therapies that include glucocorticoids and nonsteroidal anti-inflammatory medications generally not effective
  - Patients with hemodynamic instability
    - Emergent drainage
    - Pericardiocentesis or pericardiotomy with or without pericardiostomy for

instillation of long-acting nonabsorbable glucocorticoids

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CVD SYNDROMES: VALVULAR DISEASE

Endocarditis

Epidemiologic characteristics

- Relatively common complication of hemodialysis, reflecting
  - Relatively high incidence of bacteremia
  - Long-term use of dialysis catheters
  - High prevalence of pre-existing valvular abnormalities
- Mitral valve most commonly affected, followed by aortic valve

Organisms

- Most endocarditis in hemodialysis patients is secondary to Gram-positive organisms, with *Staphylococcus* species predominating

Clinical Sequelae

- Arrhythmia
- Heart failure
- Embolism
- Sepsis
- Spinal osteomyelitis or epidural abscess

Diagnosis

- Clinical presentation includes fever, murmurs, leukocytosis, and septic emboli
- Blood cultures
- Transthoracic and/or transesophageal echocardiography important in establishing diagnosis
- Imaging of the spine

Treatment

- Appropriate antibiotic therapy
- Surgical intervention indications
  - Valvular destruction
  - Progressive heart failure
  - Recurrent systemic emboli
  - Failure to respond to appropriate antibiotic therapy
- Survival often poor even with appropriate therapy
- Factors associated with mortality include
  - Hypoalbuminemia
  - Involvement of multiple valves
  - Severe valvular insufficiency

Mitral Annular Calcification

Epidemiologic characteristics

- Mitral annular calcification may occur in 30%-50% of patients on dialysis therapy and also is common in patients during earlier stages of CKD

Pathogenesis

- May be linked to altered mineral metabolism

Clinical Sequelae

- Arrhythmia
- Embolism
- Mitral valve disease
- Endocarditis
- Heart failure

Diagnosis

- Echocardiography may show uniform echodense rigid band located near the base of the posterior mitral leaflet

Aortic Calcification and Stenosis

Epidemiologic characteristics

- Aortic calcification is common in dialysis patients, occurring in 28%-55% of patients
- Dialysis patients experience aortic valve calcification 10-20 years earlier than the general population
- Valvular stenosis progresses faster in dialysis patients than in the general population
- Estimated incidence of symptomatic aortic stenosis, 3.3% per year in dialysis patients

Pathogenesis

- Age is most significant risk factor
- Abnormal mineral metabolism also may have a role

Clinical Sequelae of Aortic Calcification

- Aortic stenosis

Diagnosis of Aortic Stenosis

- Frequent episodes of intradialytic hypotension, particularly because ultrafiltration can rapidly decrease preload
- Critical aortic stenosis (cardinal symptoms include angina, heart failure, and syncope)
- Echocardiography; annual echocardiograms should be performed in those with known aortic stenosis who are:
  - Asymptomatic, but on the transplant waitlist
  - Candidates for valve replacement

Treatment

- Prevention: although not proved, control of mineral metabolism abnormalities theoretically could slow progression
- Valve replacement
  - Therapy of choice for critical aortic stenosis
  - Surgery should be performed before left ventricular contractility decreases
  - No consensus for benefit of either prosthetic or bioprosthetic valves in dialysis patients
  - In 1 study using the Society of Thoracic Surgeons National Cardiac Surgery Database, surgical mortality was higher in dialysis compared with nondialysis patients (17% vs 4%, respectively)
  - Prognosis worse if clinically indicated surgery is not performed or emergent rather than elective surgery is performed

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≫ London GM, Pannier B, Marchais SJ, Guerin AP. Calcification of the aortic valve in the dialyzed patient. *J Am Soc Nephrol.* 2000;11(4):778-783.
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CVD SYNDROMES: ATRIAL FIBRILLATION

Epidemiologic Characteristics

- Most common arrhythmia in dialysis patients, with annual incidence >10%

Clinical Sequelae

- Hypotension from loss of the "atrial kick" and cardiac synchronicity
- Thromboembolism: few data on the incidence of thromboembolism in dialysis patients

Treatment

- Rate control
  - β-Blockers
  - Calcium channel blockers
  - Digoxin, but with the caveat mentioned in the previous section
- Rate control with restoration of sinus rhythm (eg, amiodarone)
- Anticoagulation
  - Not prospectively studied
  - In a recent study, hemodialysis patients receiving warfarin for atrial fibrillation had a paradoxical increase in stroke rates; however, study is limited by selection bias
  - Benefits and risks of anticoagulation therapy in dialysis patients should be considered on an individual patient basis

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CVD SYNDROMES: VENTRICULAR ARRHYTHMIAS AND SUDDEN DEATH

Epidemiologic Characteristics

- Ventricular arrhythmias and ectopy common in patients with CKD
- During the first year of dialysis therapy, cardiac arrest rate is 93 events/1,000 patient-years
- Sudden cardiac death accounts for about 60% of all cardiac deaths in dialysis patients

- Increased frequency of sudden cardiac death on Mondays (for those dialyzing on Monday, Wednesday, and Friday) and Tuesdays (for those dialyzing on Tuesday, Thursday, and Saturday), perhaps due to hyperkalemia, hypervolemia, and volume and electrolyte shifts

Pathogenesis

- Ischemic heart disease
- Cardiomyopathy
- Rapid shifts in ions during hemodialysis, although sudden death also common in peritoneal dialysis patients
- Electrolyte abnormalities
- Increased QT dispersion
- Microvascular disease or endothelial dysfunction

Clinical Sequelae

- Sudden cardiac death

Treatment

- Similar to that in the general population
- Hemodialysis units may benefit from the presence of and training in the use of automated external defibrillators, although this has not been proved
- β-Blockers, although this has not been studied in a clinical trial
- Studies of the appropriate use of implantable defibrillators in dialysis patients are needed

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≫ de Bie MK, van Dam B, Gaasbeek A, et al. The current status of interventions aiming at reducing sudden cardiac death in dialysis patients. *Eur Heart J.* 2009;30(13):1559-1564.

≫ Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. *Semin Dial.* 2008;21(4):300-307.

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ACKNOWLEDGEMENTS

We would liked to acknowledge Daniel Weiner, MD, MS, for his help with this manuscript.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.