# Chapter 4
# Chronic Kidney Disease and Cardiovascular Risk

**Jaya P. Buddenini, Kunal Chaudhary, James R. Sowers, and Adam Whaley-Connell**

## 4.1 Introduction

There is a strong relationship between chronic kidney disease (CKD) and cardiovascular disease (CVD) risk [1–3]. The increased risk for CVD in those with CKD is heightened in the presence of traditional Framingham CVD risk factors such as type 2 diabetes, hypertension, and dyslipidemia, and the ensuing CVD contributes to a more rapid progression to end-stage renal disease (ESRD), defined as glomerular filtration rate (GFR) <15 mL/min/1.73 $m^2$ [4]. It should also be noted that the relationship between CKD and CVD events is a graded one, wherein there exists a strong linear relationship between diminishing GFR and increasing CVD events. In this context, there is an alarming trend wherein younger ESRD patients have an equivalent CVD risk equivalent to those above 65 years of age in the general population. Thereby, there is growing interest in CVD risk reduction strategies in

J.P. Buddenini
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, 3459 Fifth Avenue, 628 NW, Pittsburgh, PA 15213, USA

K. Chaudhary
Divisions of Clinical Medicine and Nephrology, Harry S. Truman Memorial Veterans' Hospital, Columbia, MO 65201, USA

J.R. Sowers
Thomas W. and Joan F. Burns Missouri Chair in Diabetes, Director of the MU Diabetes and Cardiovascular Center, Director, Division of Endocrinology, Diabetes Center, University Hospital, Columbia, MO 65212, USA

A. Whaley-Connell (✉)
Harry S. Truman Memorial Veterans Hospital, 800 Hospital Drive, Columbia, MO 65201, USA

Division of Nephrology and Hypertension, University of Missouri-Columbia School of Medicine, 800 Hospital Drive, Columbia, MO 65201, USA
e-mail: whaleyconnela@health.missouri.edu

I. Obrosova et al. (eds.), *Studies in Diabetes*, Oxidative Stress in Applied Basic Research and Clinical Practice, DOI 10.1007/978-1-4899-8035-9_4,

earlier stages of CKD not only to reduce the CVD burden but also to reduce progression of CKD [5].

The mounting evidence of the kidney cardiovascular relationship prompted the National Kidney Foundation (NKF) task force on CVD in chronic renal disease to consider CKD as a coronary artery disease equivalent for the purposes of risk stratification [6]. Moreover, the work group also recommended considering patients with CKD in the "highest-risk group" for subsequent CVD events [6]. This recommendation was largely based on findings suggesting that, even after adjusting for most traditional Framingham risk factors for CVD, the higher mortality noted in CKD subjects from CVD suggests the possible contribution of uremia-related, nontraditional risk factors [7]. This has led to an understanding of a complex association of both traditional- and nontraditional-related CVD risk factors in CKD patients. To better delineate this dynamic disease process, this chapter will focus on the pathophysiology of CVD in CKD subjects along with early identification of CKD to prevent disease progression.

## 4.2 Epidemiology

CKD is an ongoing public health dilemma affecting approximately 24–28 million, with an estimated 20 million yet unidentified, with more than one million of them receiving some form of renal replacement therapy [8, 9]. According to the United States Renal Data System 2010 annual report (USRDS), the incidence of Medicare CKD in patients aged 65 or older was 4.3 % in 2008, an increase from 1.2 % seen in 1995. The prevalence of CKD patients among Medicare patients aged 65 and older is noted to be 7.6 %, a 4.6 times increase from the rate of 1.7 % seen in 1995. The rising incident and prevalent rates for CKD are paralleled by an increasing annual cost of Medicare ESRD program in the USA approaching approximately 20.8 billion dollars. The estimated annual Medicare cost to treat patients with CKD is 57.5 billion US dollars, thus contributing to 28 % of the total Medicare expenditure [10].

## 4.3 Definition and Classification of CKD

The Kidney Disease Outcomes Quality Initiative (NKF KDOQI) established clinical guidelines in 2002 for the definition of CKD for staging purposes that continue to be adapted. The diagnosis of CKD is based on the presence or absence of structural damage to the kidney and the level of kidney function, irrespective of the cause [11]. CKD is defined as either (a) kidney damage $\geq$3 months, as confirmed by kidney biopsy or markers of kidney damage as noted by the presence of structural or functional abnormalities such as abnormal blood, urine, or imaging studies, with or without decrease in GFR, or (b)

GFR < 60 mL/min/1.73 $m^2$ for ≥3 months with or without kidney damage [11]. Staging of CKD is based on the level of GFR; stage 1 = 90–120 mL/min/1.73 $m^2$ and stage 2 = 60–90 mL/min/1.73 $m^2$ both require the presence of abnormal urine or imaging studies, wherein stages 3–5 do not; stage 3 = 30–60 mL/min/1.73 $m^2$; stage 4 = 15–30 mL/min/1.73 $m^2$, and stage 5 < 15 mL/min/1.73 $m^2$ is roughly equivalent to ESRD.

## 4.4 Pathophysiology of CKD

There are multiple risk factors that place individuals at risk for the development and more rapid progression of CKD, the most common of which are long-standing diabetes and hypertension. The pathophysiology of CKD involves a sequence of initiating events specific to the underlying etiology, leading to a set of common consequent mechanisms ultimately resulting in the reduction of renal mass and function. In those with diabetes, and to a lesser extent hypertension, there is an initial adaptive hyperfiltration mediated by elevation of glomerular capillary pressure and flow along with functional hypertrophy of the remaining nephrons. These initial adaptive responses eventually become maladaptive over a course of time and predispose to atrophy, fibrosis, and sclerosis of the remaining functional nephrons. There are numerous mechanisms that elicit the initial adaptive hyperfiltration and subsequent maladaptive tissue remodeling of nephrons such as inappropriate activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) [12].

## 4.5 CKD as Risk Factor for CVD

As compared to age-matched control subjects without kidney disease, patients with CKD have increased CVD mortality even after adjusting for traditional CVD risk factors [10–14]. The strength of this association is driven by CKD patients with GFR < 60 mL/min/1.73 $m^2$ who are at increased risk for CVD compared to those with an eGFR > 60 [13]. Further, approximately half of the mortality in ESRD patients has been attributed to heart disease [10]. However, it is important to note this is a graded, linear relationship that begins in the earliest stages of CKD with GFR approaching 120 mL/min/1.73 $m^2$ and with proteinuria. The observation the majority of individuals do not reach the requirement of renal replacement therapy (e.g., dialysis or transplantation) due to the high CVD mortality has led to an increase in scientific exploration in prevention and detection strategies [15, 16]. It is known that individuals with CKD have a high prevalence of other disorders that independently are associated with poor CVD outcomes, such as the presence of diabetes and hypertension; reduced physical activity; and

the presence of high concentration of inflammatory or oxidative biomarkers and deranged lipid parameters.

## 4.6 Traditional and Nontraditional CVD Risk Factors in CKD

The relationship between CKD and CVD is largely considered to be due to the occurrence of many common traditional Framingham risk factors such as hypertension, diabetes, dyslipidemia, and advancing age [17, 18]. However, there has been little information on successful CVD risk prediction with established equations in subjects with CKD, suggesting the presence of other risk factors that confer additional CVD risk in CKD. Uremia-related risk factors, the term first used by Sahart et al., refers to the risk factors that accumulate in CKD patients as a result of impaired renal clearance [19].

### *4.6.1 CKD and the Cardiorenal Metabolic Syndrome*

Metabolic syndrome (e.g., cardiorenal metabolic syndrome) is a constellation of metabolic abnormalities including the presence of 3 or more clinical abnormalities such as hypertension, diabetes, atherogenic dyslipidemia, abdominal obesity, and albuminuria and/or diminished renal function that are associated with a pro-inflammatory and pro-thrombotic state. This constellation of metabolic and renal disorders is a risk factor for developing both CKD and CVD. Central to the metabolic dysregulation is inappropriate activation of RAAS [20, 21] and insulin resistance with the compensatory hyperinsulinemia that contribute to inflammation and oxidative stress and the development of endothelial dysfunction [17, 22–24]. Multiple cross-sectional [25, 26] and prospective studies [27] support the association between the cardiorenal metabolic syndrome and CKD. Furthermore, the risk for CVD-related outcomes in individuals with CKD increases incrementally with each component of the syndrome (e.g., hypertension, diabetes, obesity, and dyslipidemia) [28].

### *4.6.2 Role of Common Uremia-Related Comorbidities in the Pathogenesis of CKD-Related CVD*

In addition to traditional Framingham CVD risk factors individuals with CKD possess intrinsic uremia-related risk factors such as mineral metabolism disorders, anemia, and increased levels of inflammatory and oxidative markers; abnormal

apolipoprotein levels; elevated plasma homocysteine [6]; and enhanced coagulability that independently contribute to the development of endothelial dysfunction as a precursor to CVD risk [25–31].

#### 4.6.2.1 Mineral Metabolism Disorders: Calcium and Phosphorus Metabolism

During the early stages of CKD, a diminution of 1,25-vitamin D3 formation and gut calcium absorption occurs leading to compensatory increase in parathyroid hormone (PTH). A compensated state of increased phosphorus concentration, normal serum calcium concentration, and low normal vitamin D3, along with mild to moderate increases in PTH, exists until GFR declines to <30 mL/min. As kidney disease progresses to end stage, increases in phosphorus concentration and decrease in vitamin D3 ultimately result in overt secondary hyperparathyroidism (2HPT) in the majority of individuals of CKD. Recent epidemiologic data has shown a strong clinical correlation between hyperphosphatemia and CVD mortality in ESRD patients, manifesting as vascular calcification [32]. A 41 % increase in relative risk of death from coronary artery disease has been noted with serum phosphate concentration greater than 6.5 mg/dL, as has 20 % increase in mortality from sudden death [33]. Further, increased serum phosphate concentration has been noted as an independent predictor for mortality in ESRD patients [34].

The sequential effects of disturbed mineral homeostasis are mediated by promotion of vascular calcification, bone resorption, and direct PTH toxicity [29, 32]. Hyperphosphatemia is considered a potent stimulant of intimal and medial calcification of blood vessels [35]. Intimal calcification involves formation of atherosclerotic plaque, which upon destabilization leads to an adverse cardiovascular event. On the other hand, medial calcification increases arterial stiffness, thus decreasing vascular compliance without compromising arterial lumen [36]. Numerous indices of arterial stiffness such as aortic pulse wave velocity and elastic modulus are noted to be strong independent predictors of CVD in ESRD patients [31]. This association between abnormal bone-mineral metabolism and increased vascular calcification has been suggested as the major uremia-related risk factor contributing to increased risk of CVD in CKD population.

#### 4.6.2.2 Anemia

Anemia is thought to be a contributing risk factor for cardiac remodeling leading to the development of left ventricular hypertrophy (LVH), congestive heart failure (CHF), and CVD mortality [30]. The development of anemia starts early in CKD and is multifactorial. Indeed, decreased levels of erythropoietin, iron depletion, chronic inflammation, bone marrow fibrosis, and impaired erythropoietin response are a few common causes of anemia in individuals with CKD [37]. Two different studies conducted using the National Health and Nutrition Examination Survey

(NHANES) III suggest the prevalence of anemia increases from 1 % at an eGFR of 60 mL/min/1.73 $m^2$ to 9 % at an eGFR of 30 mL/min/1.73 $m^2$ and to 33–67 % at an eGFR of 15 mL/min/1.73 $m^2$ [38–40]. Data from NHANES and the NKF's Kidney Early Evaluation Program (KEEP) support anemia in those 61 years and older with stage 3 or higher CKD [41].

Treatment of anemia with erythropoiesis-stimulating agents (ESAs) has shown to decrease LVH in CKD as well as ESRD patients on dialysis [42]. However, the use of ESAs remains controversial due to two randomized control trials, Correction of Hemoglobin and Outcomes in Renal Disease (CHOIR) [43] and Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [44], studies which do not support improved outcomes among patients' subgroups randomized to higher hemoglobin level. Further, treatment of anemia in hemodialysis patients with severe cardiac disease was associated with increased risk of death in the Normalization of Hemoglobin trial [45]. However, in another Canadian study, normalization of LV dilatation did not show any increased risk of mortality [46]. Further randomized control studies are needed to delineate whether correction of anemia, and to what level, has with CVD morbidity and mortality.

#### 4.6.2.3 Hyperhomocysteinemia

An elevated plasma homocysteine level is considered an independent CVD risk factor in the general population [6]. There are numerous conflicting studies indicating a potential role for homocysteine in CKD and CVD mortality and morbidity. Homocysteine levels are persistently elevated in ESRD patients and also in patients with cardiac diseases. Another study suggests that the antioxidant drug acetylcysteine reduces plasma homocysteine level to normal range and is associated with improvements in endothelial dysfunction and CVD events when administered long term in patients undergoing hemodialysis [47]. However, it is unclear the role the diminished kidney function and clearance has to elicit this relationship. A recent study would suggest that elevations in plasma homocysteine levels may simply be a function of reductions in GFR [48]. Thereby, further long-term interventional studies are needed to better understand the role of homocysteine for CVD risk in CKD.

#### 4.6.2.4 Inflammatory and Oxidative Stress

C-reactive protein (CRP) has been observed to be elevated in patients with kidney disease [49] and has been shown to be an independent predictor of CVD events in the general population [50]. Recent data would suggest CRP may be a marker for CVD in individuals with CKD undergoing renal replacement therapy with peritoneal dialysis, hemodialysis, or post-kidney transplant [51–54]. In earlier stages, CRP was also noted to be an independent predictor of CVD events in women with creatinine clearance <74 mL/min and with no underlying CVD [54], thereby suggesting a potential role for inflammation in the development of CVD in CKD. To

further substantiate the role of inflammation in CVD, the use of aspirin is associated with CVD risk reduction directly related to CRP levels [50].

Oxidative stress has also been noted as an underlying mechanism for CVD in CKD potentially due to ongoing low-grade inflammation and impaired antioxidant mechanisms [55]. The strength of the association between the cardiorenal metabolic syndrome and CKD underscores the significance of oxidative stress due to metabolic dysregulation in the pathogenesis of CVD in CKD due to excess reactive oxygen species [56].

The evidence derived from numerous cross-sectional, population-based, and prospective studies supports the role of uremia-related risk factors in CVD in CKD. However, a direct relationship between intervention focusing on uremic, nontraditional risk factors and CVD risk reduction has yet to be established, and further large-scale randomized controlled trials are needed to verify these associations.

## 4.7 Screening and Detection

It is not known whether population-based screening of CKD is cost-effective. In a recent study, population-based screening for CKD with assessment of estimated GFR was found to be not cost-effective in subgroups with hypertension or older people. However, targeted screening of patients with diabetes was associated with cost-effectiveness [57]. Current practice guidelines promote early screening and detection of CKD patients in order to prevent the progression of kidney disease. Several initiatives like NKF-sponsored KEEP, National Institutes of Health (NIH) Healthy People 2010, and the National Kidney Disease Education Program (NKDEP) have emphasized educating patients as well as healthcare professionals about the positive impact of early screening and diagnosis. At this point, it is conventional wisdom that a concerted team effort by primary care physicians and subspecialists is necessary to tackle this public health dilemma [58].

The NKF Kidney Disease Outcomes Quality Initiative (KDOQI) recommends screening at-risk individuals for CKD using blood pressure, GFR estimation, urine albumin to creatinine ratio, urine analysis, and imaging studies of kidneys (in select at-risk individuals) [59]. Those identified as highest risk are individuals with diabetes, hypertension, autoimmune diseases, and patients recovering from an episode of acute renal failure or with family history of kidney diseases.

The most common indices used in clinical practice for evaluation of CKD are serum creatinine (sCr) as a marker for clearance and then estimating GFR as well as determination of proteinuria. Even though sCr is the most commonly used test in clinical practice to assess renal function, sCR may not be the most accurate in early stages of kidney disease when screening and detection are critical. There are multiple reasons including biologic, pharmacologic, and estimation misclassification. In this context, rises in sCr appear only after significant loss of functioning nephrons. Moreover, the generation of sCr is based on muscle mass and diet, and the excretion or secretion of sCr is influenced by drugs such as cephalosporins,

aminoglycosides, cisplatin, cimetidine, and trimethoprim. However, estimating GFR may be the best available index for kidney function. The National Kidney Disease Educational Program (NKDEP) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and American Society of Nephrology (ASN) recommend estimating GFR from serum Cr by using either Modification of Diet in Renal Disease (MDRD) study equation or Cockcroft-Gault equation [60, 61]. Both equations take into account sCr along with age, sex, and weight variables thus minimizing the limitations of using sCr alone. However, there are limitations of the MDRD equation for estimation of GFR due to imprecision and systematic underestimation of GFR at higher levels [62]. Thereby, in 2009 a recent adaption for estimating GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [63], may overcome the limitations of MDRD in earlier stages for screening, detection, and classification of CKD.

Proteinuria is another accepted marker for kidney damage and serves as a guide for screening and detection for CKD especially in earlier stages. However, the presence of increasing levels of proteinuria in CKD is associated with a poor prognosis for both progression of CKD and the development of CVD [64, 65]. Thereby accuracy is important and measurement of albumin to creatinine ratio or total protein to creatinine ratio in untimed spot urine samples is widely accepted for assessment of proteinuria [4]. One of the earliest markers of kidney disease is microalbuminuria, defined as urinary albumin excretion between 30 and 299 mg/24 h. Annual screening allows early identification of CKD in those at highest risk and also serves as a prognostic tool [66].

## 4.8 Treatment

The treatment options for CKD patients are focused on risk factor reduction and interventions to prevent or slow the progression of CKD and importantly decrease risk for CVD-related outcomes. Treatment guidelines for risk factor reduction focus on blood pressure and glycemic control in CKD. Evidence supports that reduction in systolic blood pressure without decreasing albuminuria is insufficient in preventing the progression of CKD. Thereby, optimization of blood pressure with therapies targeting proteinuria should be a primary goal [67]. The reduction of proteinuria has shown protective effects in CVD risk in those with diabetic kidney disease [67]. Both the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) support the decreased risk of development of microalbuminuria and overt nephropathy with intensive glycemic and blood pressure control [68, 69]. However, the UKPDS further supports that blood pressure reduction may take precedence.

There is sufficient evidence to support utilizing interventions that target RAS that have shown to improve CVD-related outcomes and kidney-related outcomes in patients with or without diabetes [70]. The African American Study of Kidney Disease and Hypertension (AASK) addressed the optimal drug regimen

for African Americans with hypertensive renal disease supported by the rationale that ACE inhibitors that improved renal outcomes [71, 72]. Moreover, the Lotrel and Enalapril in African Americans with Diabetes (LEAAD) study, conducted in African American patients with both hypertension and diabetes, concluded that combination therapy with ACE inhibitor/CCB (calcium channel blocker) was much better in achieving RAS blockade and BP reduction compared to monotherapy with ACE inhibitors [73].

## 4.9 Conclusion

Recent work has clearly established a strong relationship between CKD and an increased CVD risk. In this context, the relationship is a graded linear relationship beginning at the earliest stages of CKD, thereby highlighting the importance for detection of CKD early to improve kidney-related outcomes. Current recommendations by NKF and other societies classify individuals with CKD in the highest-risk group for CVD. Recent studies in CKD population have noted the concurrent presence of uremia-related risk factors along with traditional CVD risk factors leading to the development of CVD. However this association of uremia-related risk factors is yet to be conclusively proven to establish a causal relationship. In the clinical practice, CKD is a compelling indication for aggressive blood pressure control. However, additional risk factor reduction strategies in CKD patients should be pursued by clinicians.

## References

1. Chmielewski M, Carrero JJ, Stenvinkel P, Lindholm B (2009) Metabolic abnormalities in chronic kidney disease that contribute to cardiovascular disease, and nutritional initiatives that may diminish the risk. Curr Opin Lipidol 20:3–9
2. Fried LP, Kronmal RA, Newman AB, Dild DE (1998) Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA 279:585–592
3. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S (2001) Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 134:629–636
4. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1–S266
5. Wright J, Hutchison A (2009) Cardiovascular disease in patients with chronic kidney disease. Vasc Health Risk Manag 5:713–722
6. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasishe BL, Klaq MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr (1998) Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 32:853–906
7. Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32:S112–S119
8. Dirks JH, de Zeeuw D, Agarwal SK, Alkins RC, Bennett PH, Kaseje D, Rodriquez-Hurbe B, Correa-Rotter R, El Nahas M, Katz IJ, D'Amico G, Valdes RH, Naicker S, Schieppati A, Sitthi-

Amorn C, Solez K, Viberti G, Remuzzi G, Weening JT (2004) Prevention of chronic kidney and vascular disease: toward global health equity—the Bellagio 2004 Declaration. Kidney Int Suppl 98:S1–S6
9. Lysaght MJ (2002) Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol 13:S37–S40
10. U.S. Renal Data System (2009) USRDS 2009 Annual Data Report: Atlas of end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
11. National Kidney Foundation (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43:S1–S290
12. Joanne MB, Karl S (2008) Chronic kidney disease. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (eds) Harrison's principles of internal medicine, Chapter 274, 17th edn. McGraw Hills, New York. http://www.accessmedicine.com/content.aspx?aID=2880823
13. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296–1305
14. Tesar V (2003) Cardiovascular complications in patients with chronic renal insufficiency and chronic kidney failure. Vnitr Lek 49:383–387
15. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH (2004) Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164:659–663
16. Berl T, Henrich W (2006) Kidney-heart interactions: epidemiology, pathogenesis, and treatment. Clin J Am Soc Nephrol 1:8–18
17. Coresh J, Wei GL, McQuillan G, Brancati FL, Level AS, Jones C, Klaq MJ (2001) Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med 161:1207–1216
18. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullogh PA, Kasiske BL, Kelepouris E, Klaq MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW (2003) Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 108:2154–2169
19. Sarnak MJ, Levey AS (2000) Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis 35(4 Suppl 1):S117–S131
20. Bomback AS, Toto R (2009) Dual blockade of the renin-angiotensin-aldosterone system: beyond the ACE inhibitor and angiotensin-II receptor blocker combination. Am J Hypertens 22:1032–1040
21. Ruster C, Wolf G (2006) Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol 17:2985–2991
22. Cohen AJ, McCarthy DM, Stoff JS (1989) Direct hemodynamic effect of insulin in the isolated perfused kidney. Am J Physiol 257:F580–F585
23. Dengel DR, Goldberg AP, Mayuga RS, Kairis GM, Weir MR (1996) Insulin resistance, elevated glomerular filtration fraction, and renal injury. Hypertension 28:127–132
24. McFarlane SI, Banerji M, Sowers JR (2001) Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab 86:713–718
25. Muntner P, He J, Chen J, Fonseca V, Whelton PK (2004) Prevalence of non-traditional cardiovascular disease risk factors among persons with impaired fasting glucose, impaired glucose tolerance, diabetes, and the metabolic syndrome: analysis of the Third National Health and Nutrition Examination Survey (NHANES III). Ann Epidemiol 14:686–695
26. Chen J, Muntner P, Hamm LL, Jones DW, Batuman J, Fonseca V, Whelton PK, He J (2004) The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med 140:167–174
27. Kurella M, Lo JC, Chertow GM (2005) Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 16:2134–2140

28. Kahn R, Buse J, Ferrannini E, Stern M (2005) The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 28:2289–2304
29. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM (2003) Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation 107:87–92
30. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE (1996) The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. Am J Kidney Dis 28:53–61
31. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM (2003) Aortic pulse wave velocity index and mortality in end-stage renal disease. Kidney Int 63:1852–1860
32. Block G, Port FK (2003) Calcium phosphate metabolism and cardiovascular disease in patients with chronic kidney disease. Semin Dial 16:140–147
33. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK (2001) Association of elevated serum PO(4), Ca×PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 12(10):2131–2138
34. Block GA, Hulbert-Shearon TE, Levin NW, Port FK (1998) Association of serum phosphorus and calcium×phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 3:607–617
35. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Grachelli CM (2000) Phosphate regulation of vascular smooth muscle cell calcification. Circ Res 87:E10–E17
36. Guerin AP, London GM, Marchais SJ, Metivier F (2000) Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant 15:1014–1021
37. Stevens LA, Levin A (2003) Anaemia, cardiovascular disease and kidney disease: integrating new knowledge in 2002. Curr Opin Nephrol Hypertens 12:133–138
38. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J (2002) Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med 162:1401–1408
39. Hsu CY, McCulloch CE, Curhan GC (2002) Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 13:504–510
40. El-Achkar TM, Ohmit SE, McCullough PA, Crook ED, Brown WW, Grimm R, Bakris GL, Keane WF, Flack JM (2005) Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. Kidney Int 67:1483–1488
41. McFarlane SI, Chen SC, Whaley-Connell AT, Sower JR, Vassalott JA, Salifu MO, Li S, Wang C, Bakris G, McCullough PA, Collins AJ, Norris KC (2008) Prevalence and associations of anemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis 51:S46–S55
42. Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A (1997) Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 29:541–548
43. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D (2006) Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 355:2085–2098
44. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R (2009) A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 361:2019–2032
45. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA (1998) The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339: 584–590
46. Foley RN, Parfrey PS, Morgan J, Barie PE, Campbell P, Cartier P, Coyle D, Fine A, Hainda P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA (2000) Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int 58:1325–1335

47. Tepel M, van der Giet M, Statz M, Jankowski J, Zidek W (2003) The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. Circulation 107:992–995
48. Potter K, Hankey GJ, Green DJ, Eikelboom JW, Arnolda LF (2008) Homocysteine or renal impairment: which is the real cardiovascular risk factor? Arterioscler Thromb Vasc Biol 28: 1158–1164
49. Arici M, Walls J (2001) End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int 59:407–414
50. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 336:973–979
51. Varagunam M, Finney H, Trevitt R, Sharples E, McCluskey DJ, Sinnott PJ, Raffery MJ, Yaqoob MM (2004) Pretransplantation levels of C-reactive protein predict all-cause and cardiovascular mortality, but not graft outcome, in kidney transplant recipients. Am J Kidney Dis 43:502–507
52. Noh H, Lee SW, Kang SW, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B (1998) Serum C-reactive protein: a predictor of mortality in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 18:387–394
53. deFilippi C, Wasserman S, Rosanio S, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W (2003) Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. JAMA 290:353–359
54. Knight EL, Rimm EB, Pai JK, Rexrode KM, Cannuscio CC, Manson JE, Stampfer MJ, Curhan GC (2004) Kidney dysfunction, inflammation, and coronary events: a prospective study. J Am Soc Nephrol 15:1897–1903
55. Galli F, Canestrari F, Buoncristiani U (1999) Biological effects of oxidant stress in haemodialysis: the possible roles of vitamin E. Blood Purif 17:79–94
56. Lastra G, Manrique C, Sowers JR (2006) Obesity, cardiometabolic syndrome, and chronic kidney disease: the weight of the evidence. Adv Chronic Kidney Dis 13:365–373
57. Manns B, Hemmelgarn B, Tonelli M, Au F, Chiasson TC, Dong J, Klarenbach S (2010) Population based screening for chronic kidney disease: cost effectiveness study. BMJ 341: c5869
58. Eknoyan G, Levey AS, Levin NW, Keane WF (2001) The national epidemic of chronic kidney disease. What we know and what we can do. Postgrad Med 110:23–29
59. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:1–266
60. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
61. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek WW, VanLente F (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145:247–254
62. Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, Nelson RG, Rahman M, Deysher AE, Zhang YL, Schmid CH, Levey AS (2007) Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol 18:2749–2757
63. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
64. Keane WF, Eknoyan G (1999) Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis 33:1004–1010
65. Warram JH, Gearin G, Laffel L, Krolewski AS (1996) Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. J Am Soc Nephrol 7:930–937

66. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW (2004) Nephropathy in diabetes. Diabetes Care 27:S79–S83
67. Weir MR (2005) The role of combination antihypertensive therapy in the prevention and treatment of chronic kidney disease. Am J Hypertens 18:100S–105S
68. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837–853
69. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977–986
70. Jamerson KA (2005) Preventing chronic kidney disease in special populations. Am J Hypertens 18:106S–111S
71. Agodoa LY, Appel L, Bakris GL, AASK Study Group (2001) Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 285:2719–2728
72. Wright JT Jr, Bakris G, Greene T, AASK Study Group (2002) Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 288:2421–2431
73. Flack JM, Bakris GL, McGregor J, Purkayastha D, Gatlin M, Nwose OM (2004) Safety and efficacy of combination ACE inhibitor/calcium channel blocker therapy versus ACE inhibitor monotherapy in African American patients with hypertension and type 2 diabetes. Am J Hypertens 17:180A, Abstract P-401