CJASN ePress. Published on August 11, 2015 as doi: 10.2215/CJN.04260415

Chronic Renal Insufficiency Cohort Study (CRIC): Overview and Summary of Selected Findings

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Abstract

The Chronic Renal Insufficiency Cohort (CRIC) Study is a United States multicenter, prospective study of racially and ethnically diverse patients with CKD. Although the original aims of the study were to identify novel predictors of CKD progression and to elucidate the risk and manifestations of cardiovascular disease among nearly 4000 individuals with CKD, the CRIC Study has evolved into a national resource for investigation of a broad spectrum of CKD-related topics. The study has produced >90 published scientific articles, promoted many young investigative careers in nephrology, and fostered international collaborations focused on understanding the global burden of CKD. The third phase of the CRIC Study will complete enrollment of 1500 additional study participants in 2015 and is designed to answer questions regarding morbidity and mortality in mild-to-moderate CKD and to assess the burden of CKD in older persons. This review highlights some of the salient findings of the CRIC Study in the areas of race and ethnicity, CKD progression, CKD and cognition, and cardiovascular disease outcomes; it also outlines the ongoing and forthcoming opportunities for the global nephrology community to enhance its understanding of CKD and related complications through the study.

Clin J Am Soc Nephrol 10: ●●●–●●●, 2015. doi: 10.2215/CJN.04260415

Introduction

CKD is a well-recognized public health problem affecting >20 million Americans and far more worldwide. To advance our understanding of the epidemiology of CKD, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Chronic Renal Insufficiency Cohort (CRIC) Study in 2001. Since then, the CRIC Study has recruited >5000 study participants from seven clinical centers across the United States, encompassing 13 recruitment sites. Although not randomly selected, the broad representation of age, race, ethnicity, diabetes status, and severity of disease in this cohort enables investigation of a wide range of scientific questions relevant to the United States CKD population. The original aims of the CRIC Study were to identify novel predictors of CKD progression and to elucidate the risk and manifestations of cardiovascular disease (CVD) in the setting of CKD. Over time, the scope of the study has expanded to include other areas of inquiry, including cognitive dysfunction, abnormalities of mineral metabolism, vascular function, genetics of kidney disease, frailty, ophthalmologic abnormalities, among others. This article provides a summary of selected findings reflecting the breadth of the study and highlights several major areas of future investigation.

Study Design

Details of the rationale and design of the CRIC Study, and baseline characteristics of its participants, have been described previously (1,2). In summary, the CRIC Study is a United States multicenter observational cohort study that initially recruited an ethnically and racially diverse patient population. The study protocol was approved by institutional review boards at the participating institutions and was in accordance with the ethical principles of the Declaration of Helsinki. Recruitment was completed in phase 1 of the study, between 2003 and 2008; extended follow-up was carried out in phase 2 (2008–2013). The study oversampled blacks to establish a cohort in which they were of near equal proportion to whites. Approximately 12% of study participants are of Hispanic ethnicity. Individuals with diabetes were also oversampled and comprise approximately one-half of the participants. The primary eligibility criteria were age (range, 21–74 years) and impaired renal function as defined by eGFR. Eligible participants had eGFR of at least 20 ml/min per 1.73 m^2 at entry into the study; the maximum allowable value was age-dependent (70 for participants aged 21–44 years, 60 for ages 45–64 years, and 50 for ages 65–74 years). Baseline clinical characteristics of the cohort are summarized in Table 1, overall and stratified by diabetes status.

Data on all participants were obtained through annually updated assessments of patient-reported medical histories, cognitive and behavioral health assessments, anthropometric data, electrocardiograms, and stored samples of blood and urine. Echocardiograms

Table 1. Baseline patient characteristics by diabetes status

Characteristic	Total Cohort (*N*=3939)	Diabetes (*n*=1908)	No Diabetes (*n*=2031)	*P* Value for Diabetes Versus No Diabetes
Age (yr)	58.2±11.0	59.4±9.8	57.0±11.9	<0.001
Male	2161 (55)	1064 (55.8)	1097 (54)	0.27
Race/ethnicity				<0.001
White	1638 (42)	649 (34)	989 (48.7)	—
Black	1650 (42)	848 (44.4)	802 (39.5)	—
Hispanic	497 (13)	335 (17.6)	162 (8)	—
Other	154 (4)	76 (4)	78 (3.8)	—
Household income				<0.001
≤$20,000	1240 (31)	735 (38.5)	505 (24.9)	—
$20,001–$50,000	958 (24)	455 (23.8)	503 (24.8)	—
$50,001–$100,000	734 (19)	286 (15)	448 (22.1)	—
>$100,000	392 (10)	138 (7.2)	254 (12.5)	—
Current smoker	517 (13)	224 (11.7)	293 (14.4)	0.01
Hypertension	3391 (86)	1764 (92.5)	1627 (80.1)	<0.001
MI or prior revascularization	862 (22)	534 (28)	328 (16.1)	<0.001
Congestive heart failure	382 (10)	263 (13.8)	119 (5.9)	<0.001
Peripheral vascular disease	262 (7)	193 (10.1)	69 (3.4)	<0.001
Systolic BP (mmHg)	128.5±22.2	133.6±22.8	123.7±20.4	<0.001
Diastolic BP (mmHg)	71.6±12.8	69.8±12.8	73.2±12.6	<0.001
Body mass index (kg/m^2)	32.1±7.8	34.0±8.1	30.3±7.1	<0.001
Body mass index category (kg/m^2)				<0.001
<25 (underweight or normal)	630 (16)	192 (10.1)	438 (21.6)	—
25 to <30 (overweight)	1125 (29)	459 (24.1)	666 (32.8)	—
≥30 (obese)	2174 (55)	1250 (65.8)	924 (45.6)	—
eGFR using CRIC equation	44.9±16.9	41.1±14.8	48.5±17.9	<0.001
eGFR category (ml/min per 1.73 m^2)				<0.001
<30	807 (20)	479 (25.1)	328 (16.1)	—
30 to <40	903 (23)	505 (26.5)	398 (19.6)	—
40 to <50	859 (22)	445 (23.3)	414 (20.4)	—
50 to <60	668 (17)	279 (14.6)	389 (19.2)	—
≥60	702 (18)	200 (10.5)	502 (24.7)	—
24-h urine protein (g/24 h)	0.18 (0.07–0.91)	0.38 (0.10–1.74)	0.11 (0.06–0.46)	<0.001
Use of ACEi or ARB	2689 (69)	1502 (79.3)	1187 (58.9)	<0.001
Hemoglobin A1C	6.7±1.6	7.7±1.7	5.7±0.5	<0.001

Values are mean±SD, n (%), median (interquartile range), or as otherwise indicated. MI, myocardial infarction; CRIC, Chronic Renal Insufficiency Cohort.

were obtained at least twice during follow-up, and for approximately one-third of the cohort, coronary calcification and GFR assessment by urinary clearance of ^{125}I-iothalamate was carried out every other year. Numerous additional measures (*e.g.*, carotid intima-media thickness, retinal images, ambulatory BP monitoring) were obtained on subsets of participants. A description of the frequency and components of the CRIC cohort in which selected measurements were obtained is depicted in Table 2. Major cardiovascular (CV) end points (*i.e.*, myocardial infarction, stroke, peripheral vascular disease, heart failure [HF], and atrial fibrillation) have been centrally adjudicated throughout the study on the basis of medical records and dual physician review. Renal end points examined in the study include onset of ESRD and halving of eGFR (1,2). Event rates through March 2013 for the major study outcomes are provided in Table 3.

We subsequently describe findings obtained from the CRIC Study in several areas: (*1*) race and ethnicity and CKD; (*2*) progression of CKD; (*3*) CKD and cognition; and (*4*) CV outcomes in CKD.

Race and Ethnicity and CKD

Apolipoprotein L1

Striking racial disparities exist in the United States and worldwide with respect to the occurrence and consequences of CKD. CRIC Study investigators explored the relationship between high- and low-risk variants of the apolipoprotein L1 (*APOL1*) gene and the risk of renal outcomes in individuals with diabetic and nondiabetic CKD. Blacks with high-risk *APOL1* variants, regardless of diabetes status, progressed faster to renal outcomes than those with low-risk variants. However, after adjustment for traditional risk factors and socioeconomic characteristics, blacks, regardless of diabetes status or *APOL1* genotype, had a higher risk of ESRD or halving of eGFR than whites (Figure 1). These results, in conjunction with findings from other studies, strongly support the hypothesis that the presence of high-risk variants of *APOL1* accelerates CKD progression in blacks with CKD, regardless of the cause of the underlying kidney disease. However, *APOL1* genotypes do not entirely account for the disparity in outcomes between blacks and whites (3).

Table 2. Schedule of studies/measurements performed in Chronic Renal Insufficiency Cohort Study participants

Test	Frequency of Collection[a]
Iothalamate GFR	Three measurements, each 2 yr apart[b]
24-h urine	Annually for three collections plus a final collection 2 yr later
Echocardiogram	Three measurements, each 3 yr apart
Ambulatory BP monitoring	Collected once[c]
Pulse wave velocity	Two measurements among selected participants; first measure during 2008–2010; second measure 2 yr later[d]
Coronary artery calcification	Two measurements, each 3 yr apart[b]
Ankle brachial index	Annually
Carotid IMT	Collected once[e]
Retinal imaging	Collected once[f]
Diet history questionnaire	Collected biennially until a total of four administrations

IMT, intima-media thickness.
[a]Performed in the full phase I cohort unless otherwise stated.
[b]Performed in approximately 1200 phase I study participants.
[c]Performed in approximately 1450 phase I study participants.
[d]Performed in approximately 2200 phase I study participants.
[e]Performed in approximately 920 phase I study participants.
[f]Performed in approximately 1900 phase I study participants.

Table 3. Outcome event rates in Chronic Renal Insufficiency Cohort cohort through March 2013

Outcome Events	Event Rate Per 100 Person Years			*P* Value for Diabetes Versus No Diabetes
	Total Cohort (*N*=3939)	Diabetes (*n*=1908)	No Diabetes (*n*=2031)	
ESRD or 50% decline in eGFR[a]	6.2	9.6	3.8	<0.001
MI	1.3	1.9	0.8	<0.001
CVA	0.6	0.8	0.4	<0.001
CHF	2.6	4.3	1.3	<0.001
Composite of CHF, MI, and stroke	3.8	5.9	2.1	<0.001
Atrial fibrillation	1.9	2.1	1.7	0.03
PAD	0.7	1.2	0.3	<0.001
Death	3.1	4.4	2.1	<0.001

MI, myocardial infarction; CVA, cerebrovascular accident; CHF, congestive heart failure, PAD, peripheral artery disease.
[a]eGFR using the Chronic Renal Insufficiency Cohort equation.

Racial and Ethnic Disparities in the Severity and Management of CKD and Its Related Comorbidities

The Hispanic subcohort of the CRIC Study has provided insights into ethnic disparities in CKD. Baseline data from this cohort demonstrated that Hispanics, compared with whites and blacks, had lower socioeconomic status, more advanced CKD, poorer BP control, and more severe metabolic derangements after adjustment for eGFR (4). Exploring how CKD affects mental health across racial and ethnic groups, a cross-sectional analysis demonstrated that more severe stages of CKD were associated with more clinical depression independent of race and ethnicity (5). Notably, black and Hispanic participants were less likely than whites to be treated with antidepressant therapy, both in the overall cohort and among those with clinically elevated levels of depressive symptoms (5).

Race, Socioeconomics, and Severity of Metabolic Disturbances in CKD

CRIC Study participants from racial and ethnic minority groups, who often reside in poor urban environments, are disproportionately exposed to dietary phosphate compared with their white counterparts. This difference in dietary phosphate intake might be related to limited access to fresh foods and greater availability and consumption of less expensive, phosphate-rich processed foods. An independent association was found between race and serum phosphate that was modified by income level. In the highest income stratum, blacks had significantly higher serum phosphate levels than whites, whereas in the lowest stratum (<$20,000/yr), there was no significant difference in serum phosphate levels by race (6). These findings underscore how socioeconomic disparities can influence metabolic parameters.

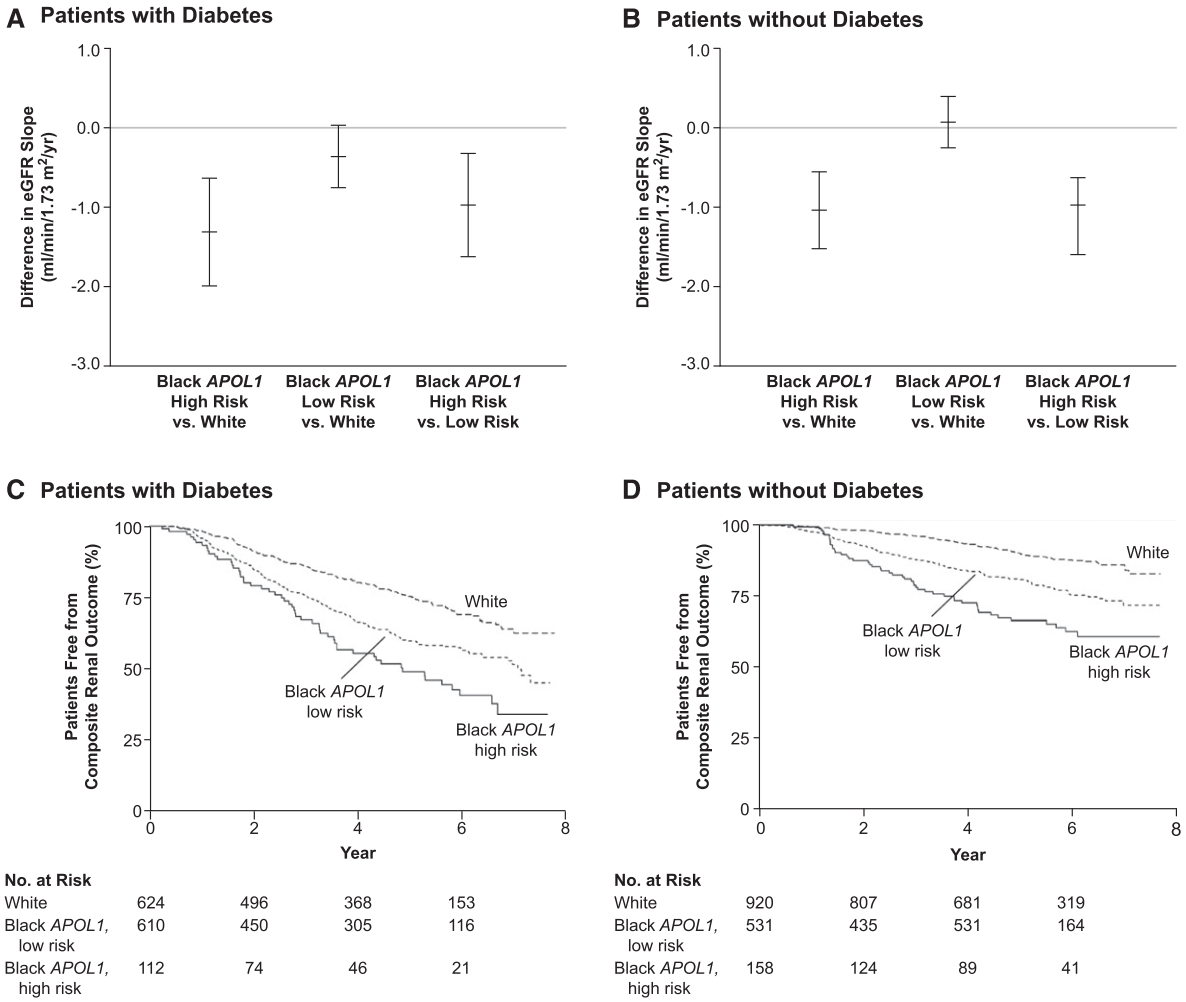

Figure 1. | Between-group comparisons of the eGFR slope and proportion of patients free from a primary outcome event in the Chronic Renal Insufficiency Cohort Study. (A) Patients with diabetes, (B) patients without diabetes, (C) patients with diabetes, and (D) patients without diabetes. In the Chronic Renal Insufficiency Cohort (CRIC) study, the primary outcomes were the eGFR slope and a composite of end-stage renal disease or a reduction of 50% in the eGFR from baseline. Shown are mean differences in the eGFR slope for black patients in the APOL1 high-risk group versus white patients, black patients in the APOL1 low-risk group versus white patients, and black patients in the APOL1 high-risk group versus black patients in the APOL1 low-risk group, among patients with diabetes (Panel A) and among those without diabetes (Panel B). In Panels A and B, the I bars indicate 95% confidence intervals. I bars that cross above the horizontal black line indicate that the difference in eGFR is not significant. Also shown are the proportions of white patients and black patients in the APOL1 high - risk and low-risk groups who were free from the primary outcome of end-stage renal disease or a reduction of 50% in the eGFR from baseline, among patients with diabetes (Panel C) and among those without diabetes (Panel D). Reproduced from reference 3, with permission.

Progression of CKD

BP and CKD Progression

Despite well-designed randomized controlled trials and observational studies, uncertainty remains regarding the optimal BP target required to mitigate CKD progression. Inherent challenges with each of these study designs limit unbiased inferences regarding the association between BP control and CKD progression, including the possibility that elevated BP is both a cause and consequence of CKD. In addition, observational studies have often been limited to a single BP measurement without incorporation of the effect of changes in BP over time.

Using annual BP measurements from the CRIC Study, marginal structural modeling was used to evaluate the association between systolic BP and renal outcomes and to overcome some of the methodologic concerns with observational studies examining the relationship between BP and kidney outcomes. Marginal structural modeling addresses some of the shortcomings of traditional observational analysis by allowing for time-updated BP measurements and adjustment for time-updated confounders, such as eGFR, proteinuria, and antihypertensive medication use (7). With this approach, the association between BP measured once and the combined outcome of ESRD or halving of eGFR was demonstrated to substantially understate the magnitude of this relationship in comparison with methods that incorporate changes in BP over time. For the single measurement model, the hazard ratio (HR) for systolic BP≥140 mmHg, compared with <120 mmHg, was 1.71 (95% confidence interval [95% CI], 1.41 to 2.08), whereas

the time-updated model demonstrated a >3-fold higher risk (HR=3.66; 95% CI, 2.58 to 5.19) (8). These results underscore the potential dynamic role of BP as a risk factor for CKD progression and highlight the likelihood that conventional analytical methods might underestimate the strength of the association.

Retinopathy and CKD Progression

Retinal pathology has been hypothesized to be a biomarker of microvascular disorders, including severity and progression of kidney disease. In a longitudinal study of the relationship between baseline retinopathy and CKD progression, there was no detectable association with the occurrence of ESRD or slope of change in eGFR after adjustment for traditional risk factors such as proteinuria and baseline eGFR (9). Despite these negative findings, detection of retinopathy remains a potentially valuable approach to identifying risk for cognitive decline as subsequently described.

Fibroblast Growth Factor 23

The CRIC Study has contributed to our evolving understanding of fibroblast growth factor 23 (FGF23) by characterizing its effect on inflammation and on CV, renal, and mortality outcomes. A longitudinal analysis explored the association between baseline FGF23 levels and the outcomes of ESRD and all-cause mortality. FGF23 levels were significantly associated with risk of ESRD after a median follow-up of 3.5 years, but the magnitude of the association was attenuated after adjustment for traditional risk factors. The association between FGF23 and ESRD also varied across strata of baseline eGFR. The association was statistically significant for those with baseline eGFR of 30–45 and >45 ml/min per 1.73 m^2, but not among those with a baseline eGFR <30 ml/min per 1.73 m^2. FGF23 was also significantly associated with all-cause mortality; in contrast with the result for ESRD, this association was robust across all eGFR strata (Figure 2) (10). These findings strongly support the notion that FGF23 mediates total mortality independent of bone mineral disease and other CKD-related comorbidities and may be a target for future clinical interventions.

Measurement of Kidney Function

A cross-sectional analysis assessed the comparative abilities of measured GFR (mGFR), eGFR (Modification of Diet in Renal Disease equation), and eGFR (cystatin C-based equation) to explain four comorbid conditions frequently observed in CKD: hyperphosphatemia, anemia, hyperkalemia, and metabolic acidosis. Neither eGFR nor mGFR was strongly associated with any of these comorbidities (C-statistics ranging from 0.69 to 0.73 across measured outcomes), and the three GFR assessment strategies performed similarly in explaining these comorbidities (11). These findings challenge the notion that mGFR is a gold standard tool for assessing the potential health effect of kidney dysfunction. Beyond investigation of the differences between eGFR and mGFR, the CRIC Study has developed an internal eGFR equation to optimize study of GFR change within the CRIC cohort (12). In addition, the CRIC Study has played an important part in the development of the

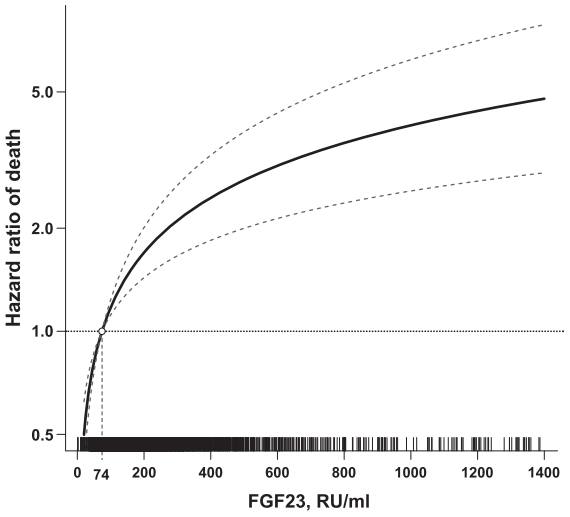

Figure 2. | Multivariable-adjusted hazard function for death according to measured (untransformed) levels of fibroblast growth factor 23. The median fibroblast growth factor 23 (FGF-23) level within the lowest FGF-23 quartile (74 relative units [RU]/ml) served as the referent value (hazard=1.0). The model was stratified by center and adjusted for age; sex; race; ethnicity; eGFR; natural log-transformed urine albumin-to-creatinine ratio; hemoglobin; serum albumin; systolic BP; body mass index; diabetes; smoking status; LDL; history of coronary artery disease, congestive heart failure, stroke, and peripheral vascular disease; use of aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; and serum calcium, phosphate, and natural log-transformed parathyroid hormone. Tick marks on the *x* axis indicate individual observations at corresponding levels of FGF-23. The solid black line represents the multivariable-adjusted hazard of mortality as a function of the measured (nontransformed) FGF-23 level. The dashed lines indicate the 95% confidence intervals. Reprinted from reference 10, with permission.

Chronic Kidney Disease Epidemiology Collaboration equation (13).

With respect to biomarkers for kidney function, the CRIC Study assayed 24-hour urine collections for neutrophil gelatinase–associated lipocalin (NGAL). NGAL is a ubiquitous lipocalin iron-carrying protein, which is heavily expressed in renal tubular cells and can be detected in the urine after ischemic kidney injury. Data from small observational studies, many cross-sectional, have suggested an association between the level of urinary NGAL and magnitude of kidney injury (14–16). CRIC Study investigators examined the association between baseline urinary NGAL levels and a composite outcome of ESRD or halving of eGFR. Higher NGAL levels were weakly associated with progression of CKD after adjustment for traditional CKD risk factors, but they did not improve prediction of kidney disease progression (model C statistic=0.85 with or without NGAL) (17).

CKD and Cognition

Although cognitive impairment is common in ESRD, less is known about its association with earlier stages of CKD. Several investigations have aimed to characterize the incidence and etiology of cognitive disorders using a subcohort of CRIC participants >55 years of age. Subcohort

participants were examined with a battery of tests, each focusing on a specific cognitive domain (*e.g.*, executive functioning, naming, attention, praxis, semantic memory). One cross-sectional analysis demonstrated a direct relationship between more severe stages of kidney dysfunction and cognitive disability. This association remained stable after multivariable adjustment across all tested domains except the category of fluency. Domains with the strongest association with renal impairment were attention and executive functioning (18). Pursuing the hypothesis that microvascular disease mediates cognitive decline in the domains of executive functioning, attention, and naming in CKD, another analysis examined the association between retinopathy in CRIC participants and cognitive impairment, finding that more severe grades of retinopathy were significantly associated with more severe cognitive impairment (19). Therefore, these data suggest that, when assessing patients with CKD, the presence of severe retinal disease might support a diagnosis of cognitive impairment in the appropriate clinical context.

CV Outcomes in CKD

CKD is a recognized risk factor for CV events (20,21), the basis for which is incompletely understood. A diverse range of CV measures have been administered to CRIC Study participants, including echocardiography, coronary artery calcium (CAC) scoring, pulse wave velocity (PWV), and carotid intima media thickness. In addition, CV outcome events are recorded after review and adjudication of medical records by trained physician reviewers using predefined diagnostic criteria.

Cardiac Structure and Function

Alterations in left ventricular (LV) structure and geometry likely predate the development of HF. A cross-sectional analysis examined echocardiographic findings among CRIC Study participants without a diagnosis of HF (22). Among participants with eGFR ≥60, 45–59, 30–44, and <30 ml/min per 1.73 m^2, the prevalence of left ventricular hypertrophy (LVH) was 32%, 49%, 57%, and 75%, respectively. In fully adjusted multivariable models, the association between eGFR and LVH remained statistically significant, highlighting the important burden of cardiac structural abnormalities among patients with CKD even in the absence of a HF diagnosis.

A recent longitudinal analysis examined the associations of incident HF with baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin T levels during a median follow-up of 5 years (23). Both of these biomarkers were strong predictors of incident HF even after multivariable adjustment. Compared with the lowest quintile of NT-proBNP, rates of incident HF increased monotonically across the remaining quintiles. Similarly, rates of incident HF increased across categories of cardiac troponin T levels compared with those with undetectable levels (Figure 3). Each of these associations was minimally attenuated after adjustment for the other biomarker, suggesting that elevations of these biomarkers are not simply a manifestation of impaired renal clearance, but may signify distinct biologic pathways leading to HF.

The CRIC Study has also demonstrated FGF23 to be a mediator of CV mortality and cardiac structural abnormalities, which may be independent of its role in bone mineral metabolism. FGF23 levels were elevated in a large component of CRIC Study participants, and these elevations were found to be independently associated with lower LV ejection fraction, higher LV mass index, a higher risk of abnormal LV geometry, and a higher risk of developing LVH (Figure 4) (24). In a cross-sectional analysis of LV metrics and eGFR, the association between LVH and eGFR was attenuated, but remained significant after adjustment for mineral and bone parameters, including FGF23, suggesting that these factors at least partially mediate the effect of renal dysfunction on cardiac abnormalities in CKD (22).

Given the risk of CV mortality among patients with CKD and ESRD, data from the CRIC Study were used to characterize the longitudinal changes in LV structure and function during the transition from advanced CKD to ESRD (25). Among 190 study participants who had an echocardiogram performed during advanced CKD and again after development of ESRD, there was a modest but statistically significant reduction in ejection fraction, suggestive of worsening cardiac function after the onset of ESRD.

Aortic Stiffness

PWV is a marker of vascular stiffness that independently predicts death and CVD in populations without CKD (26–28). Among CRIC participants, eGFR was inversely associated with PWV (29). Further, increased PWV was independently associated with a greater risk of hospitalization for incident HF (30).

New insights into a potential link between CKD and vascular stiffness were gained through studying osteoprotegerin (OPG), a protein important in regulating bone turnover (31,32), vascular calcification (31), and inflammation (33) and associated with adverse CV outcomes (34–36). CRIC participants with higher levels of OPG had increased aortic PWV (37). OPG levels were not associated with laboratory or radiologic measures of metabolic bone disease, whereas lower eGFR, older age, female sex, greater systolic BP, and lower serum albumin were all independently associated with higher OPG levels. The independence of OPG concentration from metabolic bone disease parameters suggests a direct role for OPG in the development of vascular morbidity in CKD.

Arterial Calcification

CAC correlates with atherosclerotic plaque burden and is predictive of CV events (38). To better characterize the prevalence of and risk factors for CAC in patients with CKD, a subgroup of CRIC participants underwent computed tomography scanning for CAC quantification. In a cross-sectional analysis, white race, smoking history, and presence of diabetes were found to be independent risk factors for higher CAC (39). In multivariable-adjusted models, participants with eGFR<30 ml/min per 1.73 m^2 had higher CAC levels than those with eGFR>60. In addition, greater serum calcium and serum phosphate were independent risk factors for high CAC, whereas parathyroid hormone

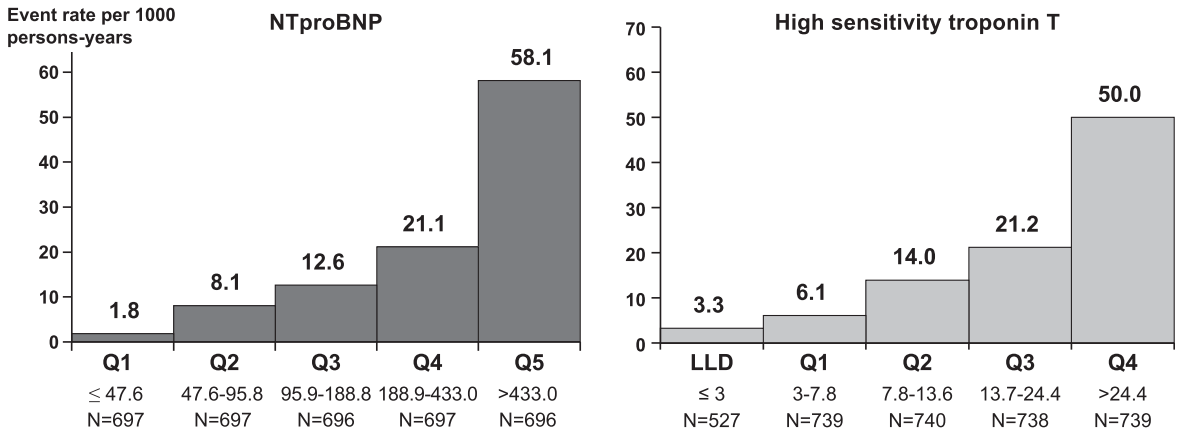

Figure 3. | **Crude rates of incident heart failure per 1000 person-years of follow-up in the Chronic Renal Insufficiency Cohort Study.** Event rates for NT-proBNP are shown by quintile; event rates for high sensitivity troponin T are shown for those with undetectable levels (≤3), and then by quartile among detectable levels. LLD, lower limit of detection; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Reprinted from reference 23, with permission.

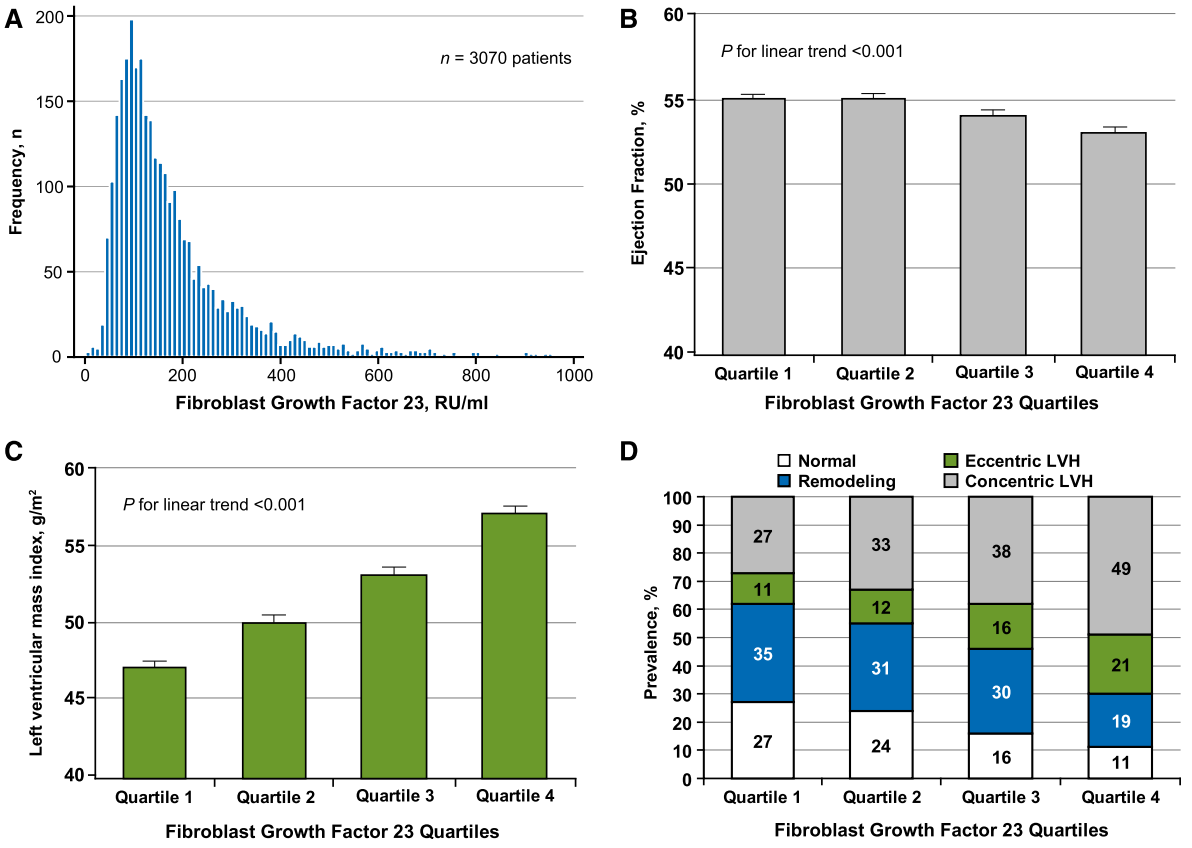

Figure 4. | **Elevated circulating fibroblast growth factor 23 levels are associated with left ventricular hypertrophy in patients with CKD.** (A) The distribution of FGF23 levels in baseline samples of 3070 participants who enrolled in the CRIC Study and underwent echocardiography 1 year later. The median FGF23 was 142 RU/ml. Fifty-eight participants with FGF23 of >1000 RU/ml (range, 1054–14,319 RU/ml), who were included in the analysis, are not shown here. (B) Ascending quartiles of FGF23 were associated with significantly decreased ejection fraction (*P* value for linear trend <0.001), but the differences between groups were modest, and the mean±SEM ejection fraction for each quartile was normal (>50%). (C) Ascending quartiles of FGF23 were associated with significantly increased mean±SEM left ventricular mass index (*P* value for linear trend <0.001). (D) With increasing quartiles of FGF23, the prevalence of concentric (gray) and eccentric (green) LVH increased at the expense of normal left ventricular geometry (white) and left ventricular remodeling (blue) (*P*<0.001). Numbers in the bars represent the percentages of prevalence for each condition. CRIC, Chronic Renal Insufficiency Cohort; FGF23, fibroblast growth factor 23; LVH, left ventricular hypertrophy; RU, relative units. Reprinted from reference 24, with permission.

level was inversely associated with CAC (40). However, neither markers of inflammation (high-sensitivity C-reactive protein, IL-6, TNF-α) nor FGF23 were independently associated with CAC. Therefore, these analyses suggest that there are separate pathways by which serum phosphate and FGF23 promote CVD in CKD. More recently, several genetic polymorphisms were found to be associated with CAC in CRIC participants and may explain some of the association between CAC and myocardial infarction (41). The potential discovery of a genetic basis for CVD in CKD represents an important step toward understanding the mechanistic basis of CV morbidity in patients with CKD.

Serum Bicarbonate and CV Outcomes

The association between serum bicarbonate and outcomes, such as renal, CV, and overall survival, has been studied in a variety of cohort studies (42–46). The CRIC Study examined these relationships prospectively. However, after adjustment for multiple comorbidities and risk factors, such as proteinuria, eGFR, and LDL, no independent association was found with atherosclerotic events or mortality (47). In contrast, there was a nonlinear association between serum bicarbonate and HF events, with a 14% higher risk of an event for every 1 mEq/L greater bicarbonate concentration >24 mEq/L (HR=1.14; 95% CI, 1.03 to 1.25). This association was not modified by diuretic use. These findings offer new perspectives on the relationship between acid-base status and CV outcomes in CKD and suggest future mechanistic studies that explore the genesis of the extremely high rate of HF among individuals with CKD.

CVD Events

The CRIC Study aims to identify novel mediators of CVD and to leverage opportunities for therapeutic targeting. Extending the studies of FGF23 and its relationship with structural cardiac changes, a longitudinal analysis demonstrated an association between higher FGF23 levels and the development of atherosclerotic events and HF clinical events (48). The association between FGF23 and HF remained statistically significant and strong after multivariable adjustment, including control for NT-proBNP and LV mass index, suggesting that LV remodeling does not fully account for this association. In totality, the observations from the CRIC Study linking FGF23 to cardiac dysfunction and HF advance the evidence base, supporting the value of examining strategies targeting the reduction of FGF23.

Ancillary Studies and International Collaborations

The CRIC Study has not only been able to examine critical questions in CKD, but it has also become a national resource promoting scholarship and training in CKD, extending far beyond the set of institutions and investigators directly following CRIC Study participants. From its inception, the CRIC Study has reached out to the broader research community, promoting a rich array of ancillary investigations led by researchers from across the nation. In addition to more than 90 published articles, the CRIC Study has fostered many ancillary studies, spanning topics from health literacy to genomics and metabolomics. Among the >70 CRIC ancillary studies funded to date and led by investigators representing >40 institutions are 32 R01s and 14 K awards (Figure 5). Among these career development awards, there have been 2 K01s, 1 K08, and 11 K23s, supporting the careers of junior investigators. These studies have expanded the scientific scope of the CRIC Study and have also leveraged its infrastructure to support the research career development of numerous young investigators. In addition, the CRIC Study has engaged many collaborative renal disease research networks in the United States and abroad, including the NIDDK's CKD Biomarkers Consortium, the CKD Prognosis Consortium, the Chronic Kidney Disease Japanese Cohort Study, and the German Study of CKD (GCKD), among others.

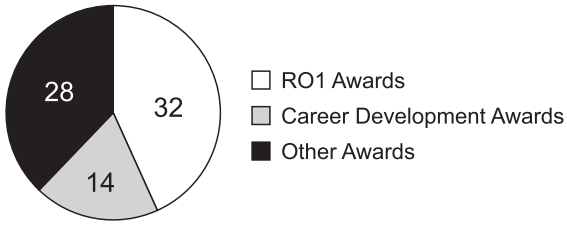

Figure 5. | Number of funded Chronic Renal Insufficiency Cohort Study ancillary studies by type of award as of June 2015.

Investigators interested in implementing ancillary studies within the CRIC Study can formally submit a proposal to the CRIC Steering Committee. Proposals are reviewed for scientific merit, feasibility, and potential overlap with other ancillary studies. On approval, investigators submit their proposals to the National Institutes of Health or other organizations for funding. A full description of the CRIC Study's ancillary study policies, the proposal template, and a listing of previously funded ancillary studies is available at the CRIC website (www.cristudy.org).

Table 4. Timing of enrollment and targeted entry criteria in phases I and III of the Chronic Renal Insufficiency Cohort Study

Characteristic	Phase I	Phase III
Timing of enrollment	2003–2008	2013–2015
No. of patients enrolled	3939	1500[a]
Age range (yr)	21–74	45–79
eGFR (ml/min per 1.73 m^2)	20–70	45–70
Proteinuria ≥1+ on dipstick (%)	Not specified	84
Diabetes mellitus (%)	50	50
Race, black/white/other (%)	45/45/10	45/45/10
Female (%)	50	50

[a]Planned enrollment.

Summary and Future Directions

These selected findings from the CRIC Study highlight the substantial effect this study has had on our understanding of renal disease progression and morbidity in CKD. The CRIC Study continues to serve as a dynamic laboratory capitalizing on emerging areas of investigation. Indeed, many of the study's findings have emerged from analyses (*e.g.*, those related to *APOL1* and FGF23) designed after the study was already well underway.

In 2013, the CRIC Study commenced enrollment of new participants for its third phase of investigation. Enrollment of an additional 1500 participants is slated to be completed in 2015. During this phase, greater emphasis will be placed on the characterization of CKD-related morbidity and mortality in mild-to-moderate disease and on the burden of CKD and its consequences in older persons. Building on the observation that the highest annual rates of renal function decline occur in the mildest stage of impairment, CRIC phase III will explore how mild-to-moderate CKD may be pathophysiologically distinct from advanced disease. The third phase of CRIC will also enroll CKD participants up to the age of 80, thereby facilitating investigation of the burden of disease among older adults with CKD, a unique and growing group of patients. Particular attention will be paid to age-related differences in functional status, frailty, cognition, quality of life, and health care resource utilization. Table 4 contrasts the study's entry criteria for phases I and III.

During this phase of the CRIC Study, collaborations with other NIDDK initiatives to promote scientific discovery and expand training opportunities continue to broaden. For example, with support from the NIDDK, the CRIC Study is collaborating with the Chronic Kidney Disease in Children Study to offer research training to junior investigators around the country to use the data environment of these two studies. International collaborations across observational studies are also anticipated in the coming years.

In summary, the CRIC Study continues to function as this nation's largest clinical research laboratory in CKD. Its ancillary studies program will continue to offer important opportunities to a growing community of investigators from around the nation. Over the last year alone, >20 additional studies have been conducted. The CRIC Study's past and on-going contributions of study data and participant biosamples to the NIDDK's research repositories (https://www.niddkrepository.org/home/) create additional opportunities for investigators to leverage the value of the study's continued careful and detailed characterization of CKD progression and its long-term consequences.

Acknowledgments

The CRIC Study Investigators additionally include Jiang He, MD, PhD Tulane University, New Orleans, LA.

Disclosures

Dr. Go has research support from Astra-Zeneca. Dr. Steigerwalt has research support from Medtronic. Dr. Hsu has received donation of biomarker reagents and measurements for research studies from Abbott. Dr. Fink serves on advisory boards for Sandoz and Relypsa. Dr. Flack has research support from Medtronic and does consulting work for Medtronic, Back Beat Medical, Medicines Company, Sanofi, Regeneron, Lundbeck, and Bayer. All other authors of this publication have no disclosures to report.

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M.D. and S.B. contributed equally to this work.

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.04260415/-/DCSupplemental.