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The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods

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Abstract. Insights into end-stage renal disease have emerged from many investigations but less is known about the epidemiology of chronic renal insufficiency (CRI) and its relationship to cardiovascular disease (CVD). The Chronic Renal Insufficiency Cohort (CRIC) Study was established to examine risk factors for progression of CRI and CVD among CRI patients and develop models to identify high-risk subgroups, informing future treatment trials, and increasing application of preventive therapies. CRIC will enroll approximately 3000 individuals at seven sites and follow participants for up to 5 yr. CRIC will include a racially and ethnically diverse group of adults aged 21 to 74 yr with a broad spectrum of renal disease severity, half of whom have diagnosed diabetes mellitus. CRIC will exclude subjects with polycystic kidney disease and those on active immunosuppression for glomerulonephritis. Subjects will undergo extensive clinical evaluation at baseline and at annual clinic visits and via telephone at 6 mo intervals. Data on quality of life, dietary assessment, physical activity, health behaviors, depression, cognitive function, health care resource utilization, as well as blood and urine specimens will be collected annually. ^{125}I-iothalamate clearances and CVD evaluations including a 12-lead surface electrocardiogram, an echocardiogram, and coronary electron beam or spiral CT will be performed serially. Analyses planned in CRIC will provide important information on potential risk factors for progressive CRI and CVD. Insights from CRIC should lead to the formulation of hypotheses regarding therapy that will serve as the basis for targeted interventional trials focused on reducing the burden of CRI and CVD.

The rate of ESRD has increased steadily in the United States over the past three decades. Insights into the epidemiology and treatment of ESRD have emerged from many investigations including those conducted by the United States Renal Disease System. Much less is known about the epidemiology of pre-ESRD chronic renal insufficiency (CRI), especially the relationship between CRI and cardiovascular disease (CVD).

CRI has been recognized as a silent epidemic (1) affecting more than ten million Americans. The burden of morbidity and mortality from CRI derives from the progression of CRI to ESRD and the disproportionate risk of CVD in the setting of CRI. CRI is strongly and independently associated with CVD, even after adjustment for traditional CVD risk factors. These findings led to the hypothesis that specific "uremia-related risk factors" augment the rate of CVD (2) and cause many patients with CRI to succumb to fatal cardiovascular events before needing renal replacement therapy.

The National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) established the Chronic Renal Insufficiency Cohort (CRIC) Study in 2001 to improve understanding of the relationship between CRI and CVD. The CRIC Study goals are to examine risk factors for progression of CRI and CVD among patients with CRI and develop predictive models to identify high-risk subgroups, informing future treatment trials and increasing application of available preventive therapies. Improved recognition of etiological factors will permit development of interventions to reduce the burden of advanced renal failure and cardiovascular morbidity and mortality. The CRIC Study will address five principal hypotheses:

1. A set of nontraditional risk factors is associated with both progression of CRI and development of ESRD. (Nontraditional risk factors indicate factors that have not yet been well studied in renal disease in contrast to well studied factors such as BP and proteinuria.)

See complete list of CRIC Study investigators at the end of this document.
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2. A set of nontraditional risk factors is associated with subclinical measures of CVD progression and clinical events, and measures of CVD progression in the setting of CRI.
3. Risk factors for CRI progression and CVD in the setting of CRI vary by demographic characteristics and the presence of diabetes mellitus.
4. Morbidity and complications associated with CRI and its progression diminish global and disease-specific quality of life, impair functional status, and increase health care resource utilization.
5. Progression of CRI as estimated by serum creatinine and currently available serum creatinine-based formulae yield biased estimates of the rate of progression of CRI.

Materials and Methods

Study Organization

The CRIC Study consists of a Scientific and Data Coordinating Center (SDCC), in Philadelphia, Pennsylvania; seven clinical centers (Ann Arbor, Michigan; Baltimore, Maryland; Chicago, Illinois; Cleveland, Ohio; New Orleans, Louisiana; Philadelphia, Pennsylvania; and Oakland, California); central laboratories for analysis of GFR and biochemistries; three central reading centers (coronary calcium measurement, echocardiography, and electrocardiography); a Scientific Advisory Committee; and NIDDK project scientists.

Study Design

Each clinical center will enroll approximately 430 to 500 individuals over a 33-mo period to establish a cohort of 3000 participants. Participants will be followed until death or dropout from the study. Follow-up will continue even after ESRD occurs.

Cohort Participants

The CRIC Study will include a racially and ethnically diverse group of adults with a broad spectrum of renal disease severity, half of whom will have diagnosed diabetes mellitus, the remainder having a broad array of nondiabetic renal disease.

Patients aged 21 to 74 yr with CRI will be enrolled in the CRIC Study. The upper age limit of 74 yr ensures the ability to evaluate progression and implications of renal dysfunction in older patients who are at greatest risk of cardiovascular events, but largely have been excluded from previous studies. The age distribution also should include sufficient numbers of younger individuals with CRI whose rates of death due to nonrenal/CVD etiologies and other noninformative censoring events are expected to be low.

Race/Ethnic Distribution. The CRIC Study anticipates a demographically heterogeneous group of participants (Table 1). Key materials will be translated into the most common languages, and efforts are being made to have bilingual personnel at relevant clinical centers.

Age-Based Estimated GFR Inclusion Criteria. Age-related entry criteria for GFR were established (Table 2) to limit the proportion of older individuals recruited with age-related diminutions of GFR, but otherwise nonprogressive CRI. The estimated GFR to define eligibility is based on the simplified MDRD estimating equation (GFR [ml/min per 1.73 m^{2}] = 186 × [serum Cr (mg/dl)]$^{-1.154}$ × [age]$^{-0.203}$ × [0.742 if female] × [1.212 if black]) (3), using locally measured serum creatinine calibrated to a central laboratory. This process minimizes the effects of assays performed at different laboratories (4).

Exclusion Criteria. Other than a known diagnosis of polycystic kidney disease**,** no specific renal diagnoses will be excluded. However, data will be recorded to characterize the presumed etiology of underlying renal disease. Polycystic kidney disease is excluded because of the distinct, specific pathophysiology underlying this condition. Furthermore, other NIH research initiatives are presently focusing on this condition. Patients on active immunosuppression for glomerulonephritis also will be excluded.

Table 1. Anticipated race ethnic target distribution in CRIC Study

Race/Ethnic Group	Final Proportion of CRIC (%)
Caucasian	50
African American/Black	40
Latino/Hispanic, Asian/Pacific Islander, and other	10

Table 2. Summary of CRIC Study sample characteristics

Age stratum	Eligible Estimated GFR Range (ml/min 1.73 per m^{2})[a]	No diabetes (%)	Diabetes (%)
21 to 44 yr	20 to 70	12.5	12.5
45 to 64 yr	20 to 60	25	25
65 to 74 yr	20 to 50	12.5	12.5

[a] Based on simplified MDRD equation (3).

Recruitment

Subject recruitment will vary by clinical center. The recruitment goal of 3000 requires approximately 450 participants from each clinical center (including replacement of dropouts during the first year, anticipated to be as high as 5%) (5,6). Most clinical centers can access at least one large database to identify individuals with elevated serum creatinine levels. Recruitment also will occur at clinics enriched with cases of CRI. Securing local physician approval and contacting potential screenees depend on local institutional review boards' guidelines and the requirements of each medical facility.

Screening and Enrollment

Eligible persons will be evaluated at baseline when detailed sociodemographic information, medical and family history, medications used in the previous 30 d, anthropometric measures (weight, height, midabdominal circumference), resting BP, heart rate, physical evidence of peripheral vascular disease, and ankle-brachial index will be collected. In addition, blood specimens will be obtained, and a 24-h urine sample collection will be initiated. ^{125}I-iothalamate clearances will be scheduled for one-third of all participants. Questionnaires concerning quality of life, dietary assessment, physical activity, health behaviors, depressive symptoms, cognitive function, and health care resource utilization will also be administered.

Follow-Up and Retention

Retention strategies that should enhance the attractiveness of long-term participation include free medical testing, frequent contact with participants via personalized mailings, telephone calls, newsletters

and educational sessions, and reimbursement of time and travel expenses.

Participants will return annually for in-person follow-up visits. Participants will be contacted by telephone at the 6-mo interval between clinic visits and queried about study outcomes and updates on general health and contact information. Newsletters and information regarding CRI and CVD will supplement in-person and telephone contacts. Consistent with other cohort studies (*e.g.*, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study) up to 3 to 5% of participants may be lost to follow-up annually. Persistent efforts will be made to prevent participant dropout. The National Death Index will be searched periodically for all participants lost-to-follow-up to ensure complete vital status information.

Collection of Study Data

Plasma and urine samples will be collected annually and stored. These specimens will enable exploration of biomarkers for lipid metabolism, inflammation, coagulation status, oxidative stress, endothelial function**,** among others, as predictors of the progression of CRI and CVD. Blood samples will also be collected to extract DNA for future genetic studies.

Study Outcomes: Renal

The primary renal outcome is progression of CRI defined by reduction in estimated GFR. Renal events are defined as the need for renal replacement therapy (ESRD), an estimated halving of GFR, and/or a 25 ml/min per 1.73 m^2 decline in GFR from baseline. In the whole cohort, estimated GFR is based on the MDRD formula which relies on serum creatinine, pending development of a GFR estimating equation derived from CRIC Study data (3). This equation will be developed among the ^{125}I-Iothalamate subcohort, based on serum creatinine as well as other biologic measures (*e.g.*, serum albumin, serum cystatin C, measures or estimates of body composition) and clinical characteristics (*e.g.*, age, gender, race, and diabetes status). Iothalamate-based clearance measurements are needed because of certain gaps in our knowledge of the accuracy of estimating equations in some patient groups over time.

Study Outcomes: Subclinical CVD

Evaluation of subclinical CVD in different vascular beds as well as assessment of cardiac structure and function will be performed at years 1 and 4 of follow-up. These evaluations include standard 12-lead surface electrocardiography (ECG) and echocardiography (echo) in all participants, and coronary arterial calcification using electron beam or spiral CT in one-third of participants.

Identification and Adjudication of Clinical Cardiovascular Outcomes

Clinical centers will query participants or their proxies every 6 mo about possible CV hospitalizations, and outpatient CV tests and interventions. Deaths are classified as cardiac, noncardiac, or unknown. CV events such as myocardial infarction, stroke, new onset or worsening congestive heart failure, and others will be identified.

Myocardial infarction is defined as typical rise and gradual fall, or typical rise in cardiac troponin levels and rapid fall of CK-MB enzymes combined with symptoms or other manifestations of myocardial ischemia or ECG changes compatible with ischemia or infarction (7). Infarction will also be indicated by new fixed perfusion abnormalities with corroborating wall motion or ECG changes. Congestive heart failure (CHF) is defined as hospital admission for new or abrupt worsening of signs and symptoms accompanied by falling cardiac output. Serious cardiac arrhythmias are defined as the presence of sustained cardiac rhythm disturbances such as ventricular tachycardia, ventricular fibrillation, symptomatic bradycardia, atrial fibrillation/flutter, *etc.*

Stroke is defined as a fixed (>24 h) acute neurologic deficit using Trial of Org 10172 in Acute Stroke Treatment (8) and the CARE Study Classification of Subtypes of Acute Ischemic Stroke criteria (9) for stroke classification. Cerebrovascular revascularization procedures will include surgery or percutaneous interventions in the cerebrovascular circulation. Peripheral vascular disease is defined as amputation due to vascular disease or peripheral surgical or percutaneous revascularization.

Statistical Considerations

Research questions will be analyzed separately in diabetic and nondiabetic participants and overall, unless there is statistical evidence of interaction by diabetes status or a strong biologic evidence for an interaction. Failure-time, repeated measures, and nested analyses will be the principal analytical approaches. Several main study endpoints are failure-times: CVD events and clinically important reductions in renal function (*e.g.*, ESRD and/or significant declines in estimated GFR). Kaplan Meier curves and Cox proportional hazards analysis will be the principal statistical approaches using standard procedures to assess underlying assumptions and adequacy of fit of multivariable models (10–12). Proportional hazards analysis also will be used to explore the joint effects of treatments or exposures received at different times on the rate of failure using weighted estimation of marginal structural models (13) and G-estimation of structural nested models (14).

Analysis of repeated measures (*e.g.*, GFR) will use standard mixed effects growth curve models supplemented by generalized estimating equations that allow for the estimation of individual participants' slopes and intercepts, and for comparison of subgroups defined at baseline and over time. Analytical approaches will account for non-independence of repeated measurements from individual participants and missing data (15,16).

Statistical methods will accommodate staggered entry and different lengths of follow-up among subgroups, and permit evaluation of bias introduced by differential follow-up. Characteristics of participants without complete follow-up will be examined and factors associated with drop-out will be modeled.

Analyses of selected biomarkers, ^{125}I-iothalamate clearance, and coronary calcification, collected or analyzed only on a random subset of participants will resemble those of other repeated measures. For these analyses, multiple imputation (17) also will be considered for dealing with missing data on variables in participants not in the subcohort.

Event-based analyses will supplement analyses of GFR as a continuous, repeated outcome measure. Participants will be considered to have failed if they either develop ESRD or experience a substantial decrease in GFR. These analyses will supplement the primary analysis examining change in equation-based estimated GFR criterion as a substitute for the directly measured ^{125}I-iothalamate clearance criterion; the estimates will derive from GFR prediction equations developed using study data.

Certain biomarkers will be available from all participants by analyzing blood samples that are stored and frozen at annual visits. Analysis of these data to look at the associations of predictor variables and outcomes will use the case-cohort approach of Prentice (18) that permits estimation of relative hazards. The efficiency of this approach can be improved by weighting methods that can allow inclusion in the

analysis of participants who do not develop the outcome of interest (19).

Statistical Power

The CRIC Study will have ample statistical power for time-to-event and repeated measures analyses. For a sample size of 1500, the size of the diabetic and nondiabetic subgroups, an exposure prevalence of 0.1 and 0.5, the CRIC study will have 80% power to detect a hazard ratio of approximately 1.80 and 1.60, respectively. Analogously, the study will have 80% power to detect a difference in slope of change in GFR of 0.6 and 0.4 ml/min.

Discussion

The NIDDK developed the CRIC Study in response to the epidemic of CRI and the acknowledgment that existing studies of CRI and ESRD provide an incomplete understanding of the burden of CRI. Morbidity and mortality associated with CRI, often from CVD, make the long-term study of afflicted individuals compelling because in certain individuals CRI may not progress to ESRD, or because mortality from competing illness, typically, CVD occurs.

The CRIC Study represents a major commitment to use observational epidemiology to address research questions regarding etiology, prognosis, therapy, health services utilization, and quality of life among patients with both diabetic and nondiabetic CRI. In the CRIC Study, analogous to the Framingham Heart and the ARIC studies, the NIDDK has established a unique resource that will explore long-term consequences of CRI, as well as suggest novel mechanistic hypotheses. Providing a clinical laboratory for this disease which progresses in a variable, but often protracted time-frame will enable such goals.

Until now, most follow-up data on CRI have come from clinical trials of patients with CRI and from large-scale cohort studies conducted in which CRI was not a primary focus. Although selective enrollment and limited scope of risk factor data narrow the extent of inferences from these studies, data from these studies complement the CRIC Study.

In the Hypertension, Detection, and Follow-up Program (HDFP), baseline serum creatinine >1.7 mg/dl was associated with a 2.2-fold higher adjusted odds of death at 8 yr compared with baseline serum creatinines <1.7 mg/dl (20). Consistent with these findings, the Cardiovascular Health Study reported an adjusted mortality rate 71% higher among 5000 participants with baseline serum creatinine ≥ 1.5 mg/dl (21). Both small amounts of proteinuria and elevated creatinine have independently been associated with increased CV mortality in a representative sample of the general population (22).

Other studies have indicated the extent to which the increase in the rate of death in the setting of CRI is due to CVD. Jungers *et al.* (23) observed a two- to threefold higher rate of MI among 147 patients with CRI compared with the incidence in the French general population. CV events were independently associated with tobacco use, hypertension, elevated fibrinogen and homocysteine, and low HDL cholesterol. Secondary analyses of the MDRD study demonstrated the large burden of CVD in the setting of CRI, finding that 25% of first hospitalizations were for CVD (24). Two trials of angiotensin converting enzyme inhibitors in nondiabetic CRI provided data on the rate of the combined endpoint of sudden death and MI. Among patients with a serum creatinine between 1.5 and 4.0 mg/dl, there was a rate of 1% per year with the use of benazepril (25), similar to that observed among patients with >3 g/d proteinuria enrolled in the REIN Study (26).

More recently, Culleton *et al.* (27) reported on 6233 adults in the Framingham Heart Study. The rate of all-cause mortality and CVD was compared between participants with normal and mild CRI (serum creatinine ≥ 136 umol/L in men and ≥ 120 umol/L in women). The adjusted rate ratios for all cause mortality were 1.31 (95% CI: 1.02 to 1.67) for men and 1.08 (95% CI: 0.87 to 1.34) for women. The adjusted rate ratios for CVD were 1.06, 95% CI (0.79 to 1.43) for men, and 1.04, 95% CI (0.79 to 1.37) for women. These studies provided compelling evidence for the morbidity risks of CRI beyond simple progression to ESRD. However, full understanding of the relationship between CRI and CVD awaits research that examines biomarkers of putative mechanistic pathways and uses more sensitive tools to detect CVD such as EBCT or echocardiography.

Concurrent with CRIC are at least four longitudinal studies that are exploring risk factors for progression of CRI. The National Health and Nutrition Examination Survey (NHANES) collects data on the prevalence of nephrologic conditions in the US population, and the association between kidney disease and conditions including diabetes and hypertension, and monitors kidney disease prevalence and risk factors over time. The African American Study of Kidney Disease (AASK) Cohort Study investigates environmental, socioeconomic, genetic, physiologic, and other comorbid factors that influence progression of kidney disease in a cohort of African Americans with hypertensive kidney disease. KEEP 3.0, a longitudinal cohort study supported by the National Kidney Foundation, will begin in 2003, and will enroll 6900 participants at risk for kidney disease from 15 sites. KEEP 3.0 participants will be followed over 3 yr to evaluate progression of kidney disease and the effect of provider and participant educational interventions on disease progression. The planned Canadian Prevention of Renal and Vascular Events Trial in Chronic Renal Disease (CAN-PREVENT) is a randomized clinical trial of intensive cardiovascular risk factor interventions compared with usual care in Canadian patients with moderate CRI. In all instances, the CRIC Study will extend or expand on these studies with respect to types of renal disease and mechanistic pathways under study, and use of state-of-the-art tools to track the progression of CRI and CVD.

Interventional studies designed to prevent the progression of CRI can only occur after gaining sufficient knowledge of the burden of disease, its natural history, and its putative mechanisms. CRIC will provide important information on potential risk factors for progressive CRI and CVD as did studies of the relationship between cholesterol and hypertension to CVD before treatment trials of lipid-and BP-lowering drugs. CRIC should provide this knowledge, allowing formulation of hypotheses regarding therapy that will serve as the basis for

targeted interventional trials focused on reducing the burden of CRI and CVD.

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