

The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study: Objectives, Design, and Methodology

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Background and objectives: Children and adolescents with chronic kidney disease (CKD) are at high risk for cardiovascular morbidity and mortality. A systemic arteriopathy and cardiomyopathy has been characterized in pediatric dialysis patients by the presence of morphologic and functional abnormalities.

Design, setting, participants, & measurements: The Cardiovascular Comorbidity in Children with CKD (4C) Study is a multicenter, prospective, observational study aiming to recruit more than 600 children, aged 6 to 17 years, with initial GFR of 10 to 45 ml/min per 1.73 m². The prevalence, degree, and progression of cardiovascular comorbidity as well as its association with CKD progression will be explored through longitudinal follow-up. The morphology and function of the heart and large arteries will be monitored by sensitive noninvasive methods and compared with aged-matched healthy controls. Multiple clinical, anthropometric, biochemical, and pharmacologic risk factors will be monitored prospectively and related to the cardiovascular status. A whole-genome association study will be performed to identify common genetic variants associated with progression of cardiovascular alterations and/or renal failure. Monitoring will be continued as patients reach end-stage renal disease and undergo different renal replacement therapies.

Results: While cardiovascular morbidity in adults is related to older age and additional risk factor load (e.g., diabetes), the role of CKD-specific factors in the initiation and progression of cardiac and vascular disease are likely to be characterized with greater sensitivity in the pediatric age group.

Conclusions: The 4C study is expected to provide innovative insight into cardiovascular and renal disease progression in CKD.

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Children and adolescents with chronic kidney disease (CKD) are at high risk for cardiovascular events (1). In young adults with end-stage renal disease, cardiovascular mortality is increased 500- to 1000-fold compared with the general population (2).

Young CKD patients usually do not present with clinical symptoms of cardiovascular disease (CVD). Ischemic heart disease and myocardial infarction are very rare in childhood. However, even children may present with subclinical CVD, and significant structural and functional changes of the heart and the large arteries can be detected by sensitive methods (3,4).

Recently, noninvasive measurements of vascular morphology and function such as carotid artery intima-media thickness (cIMT), pulse wave velocity (PWV), and the pulse wave augmentation index (AI) have been established as valid surrogate markers of arteriopathy in adult CKD patients (5). Similar to echocardiographic findings (6), these surrogate markers are highly predictive for future cardiovascular events.

The pediatric population appears uniquely suited to study the effects of CKD on the cardiovascular system due to the

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virtual absence of vascular morbidity related to aging, diabetes, and smoking. However, the factors underlying early cardiovascular morbidity in CKD and their relative contribution are poorly understood. Moreover, the natural evolution of cardiovascular lesions and their relationship to kidney disease progression are largely unknown due a lack of prospective observational studies in a sufficiently large cohort of pediatric CKD patients.

To improve our understanding of the causes and consequences of cardiovascular comorbidity in children with CKD, a consortium of pediatric nephrologists in Europe has joined to perform a long-term prospective observational study monitoring the cardiovascular health of children as they advance through successive stages of CKD. The Cardiovascular Comorbidity in Children with CKD (4C) Study will follow up to 625 patients in more than 50 pediatric nephrology units in 14 European countries (<http://www.4c-study.org>).

Materials and Methods

Objectives

The 4C Study will systematically evaluate the prevalence, clinical symptoms, and progression of cardiovascular and kidney disease and assess the impact of potential risk factors, as well as the influence of genetic variables on disease progression.

Measurements of morphologic and functional characteristics of the heart and large arteries will serve as surrogate end points for CVD in this study.

The morphologic end points are the progression of cIMT and left ventricular mass index (LVMI). The functional end points are progression of local (stiffness of carotid artery) and systemic arterial stiffness (PWV) and myocardial dysfunction (tissue Doppler).

Possible associations of these end points with multiple potential clinical, anthropometric, biochemical, and pharmacologic risk factors

will be explored. We aim to develop and validate a clinically applicable individual cardiovascular risk score.

Furthermore, possible genetic risk factors for early manifestation of progressive vascular lesions and progressive kidney disease might be identifiable by genome-wide single-nucleotide polymorphism (SNP)-screening and haplotype analysis.

Study Organization (Figure 1)

Patients meeting the inclusion criteria will be enrolled by local investigators. The course of estimated GFR (7) and proteinuria will be followed every 6 months. Every 12 months, the patients will undergo a detailed cardiovascular assessment comprising sonographic assessment of cIMT and elasticity, PWV, AI, left ventricular mass and contractility, 24-hour BP monitoring, as well as profiling of serum markers. A blood sample for DNA analysis will be obtained at a single time point.

Eight investigators will serve as regional coordinators. Each coordinator will be responsible for the acquisition of data and biomaterials in 5 to 10 study centers and will perform the sonographic assessments and pulse wave studies at the individual centers once per year. To guarantee optimal reproducibility and quality of the investigations, the coordinators will be thoroughly instructed in the use of the diagnostic methodologies in several joint training sessions before start of the study. Echocardiographic assessments will be performed either by a local cardiologist or by the regional coordinator. Biosamples will be collected by the regional coordinators and stored in a central biorepository. Regular investigator meetings will be held to synchronize study activities, discuss results, and exchange experiences.

Patient follow-up will be continued when end-stage renal disease is attained and renal replacement therapy started. The evolution of cardiovascular risk factors, function, and morphology will be evaluated prospectively by structured subanalysis in patients undergoing maintenance dialysis (4C-D substudy) and pre-emptive or postdialysis transplantation (4C-T substudy).

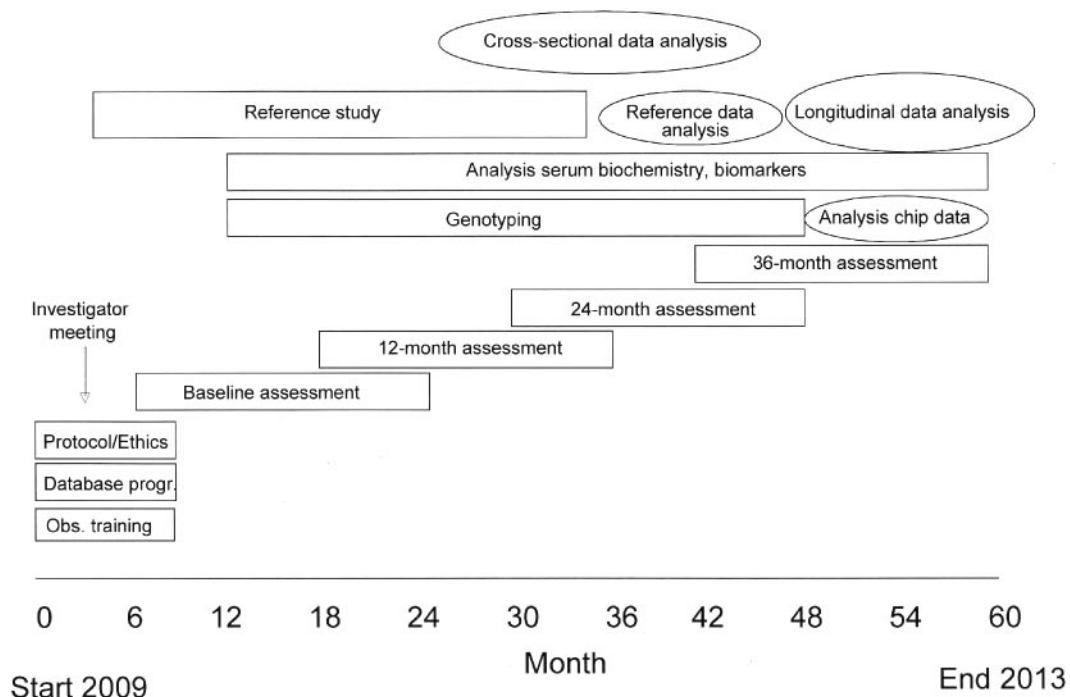


Figure 1. Study flow chart.

The 4C Study is funded by the KfH Foundation for Preventive Medicine. This nonprofit organization provides support for selected prospective observational studies in the field of CKD in Germany (<http://www.kfh-stiftung-praeventivmedizin.de/>). A core set of clinical and laboratory data will be collected in each funded study and submitted to a central database for integrative analysis. All studies are reviewed annually by a steering committee.

Study Population

The 4C Study is a prospective observational cohort study in pediatric CKD patients. Inclusion criteria are age 6 to 17 years and estimated GFR 10 to 45 ml/min per 1.73 m². Exclusion criteria are the presence of active systemic vasculitis, renal vascular anomalies, coexisting primary cardiovascular anomalies, and anomalies of the limbs preventing diagnostic procedures. Children who reach end-stage renal disease will be continuously followed while on renal replacement therapy.

It is planned to follow the patients throughout childhood until transition to an adult treatment center. The study will be continued for at least 3 years, with a possible extension to 8 years if funding can be secured.

After the end of the funded period, it is planned that patients will be followed in a registry of cardiovascular and renal disease progression, in which any locally available clinical, anthropometric, and biochemical screening parameters will continue to be documented through attainment of adult age.

Clinical and Laboratory Methods

Cardiovascular Monitoring (Table 1)

Carotid sonography will be performed using local ultrasound devices. Device settings and measurement parameters as well as the examination procedures will be standardized according to international radiologic consensus recommenda-

tions (8). All sonography findings will be documented digitally and cross-validated in a blinded manner. This will guarantee a maximum of objectivity and minimize the residual interobserver-variability.

ECGs and echocardiographies will be performed by the local pediatric cardiologists, standardized according to the guidelines of the American Society of Echocardiography. Whenever possible, additional tissue doppler imaging will be performed. All evaluations will be video-documented and centrally analyzed.

All centers are equipped with ambulatory BP monitoring devices (Spacelab ABPM device 90207-2Q; Spacelabs Medical, Issaquah, WA).

Standard operating procedures for ABPM have been placed on the study web site for continuous reference by participating centers.

Coronary calcification will be evaluated by multislice computed tomography (CT) scan if available in the individual centers (optional).

Biochemical Monitoring, Analysis of Biomarkers for CVD

Blood samples will be aliquoted, and analyses of biochemical parameters will be performed in a central laboratory (Synlab, Heidelberg). Biomarker analyses will be performed in several specialized laboratories.

Genome-Wide Association Study

Genome-wide screening will be performed using the Affymetrix 6.0 SNP Chip containing more than one million SNP

Table 1. Synopsis of data obtained in the 4C Study

Cardiovascular monitoring (annual intervals)	a. Sonography of the intima-media thickness (morphology, B-Mode) and elasticity (function, M-Mode) of the common carotid artery. b. Pulse wave velocity and augmentation index. c. Echocardiography, ECG. d. Ambulatory 24-hour blood pressure monitoring (ABPM). e. Optional: Coronary CT (every 2 year).
Clinical and anthropometric measurements	
At time of enrollment:	Baseline evaluation (<i>e.g.</i> , patient data, renal and extra-renal diagnoses, gestational age, birth weight and length, cardiovascular medical history of patient and family).
At 6-month intervals:	Height, weight, BMI, pubertal stage, current medication.
At 12-month intervals:	Body composition analysis (by multifrequency bioelectrical impedance analysis).
Monitoring of renal function:	
At 6-month intervals:	Estimated GFR (plasma Cystatin C clearance), serum creatinine, urinary protein excretion.
Biochemical and biomarker monitoring (blood testing)	
At 12-month intervals:	Serum lipid profile, ultrasensitive CRP, uric acid, 1,84-/7,84-PTH, 25-OH-Vit.D3, 1,25-Vit.D3, osteoprotegerin, fetuin-A, homocysteine, ADMA, adiponectin, leptin. Biomarkers of oxidative and carbonyl stress.

markers for haplotype analysis. Hybridization and analysis of the chips will be performed at the Cologne Center of Genomics.

Data Acquisition and Handling

All clinical data obtained at the 6-month patient visits are regularly transmitted to the central database by online data entry via the study web site. Laboratory results will also be transmitted electronically and stored in the central database on a central server at Heidelberg University Computing Facilities. The web site and database will be on a secure server containing a public and a password-protected domain.

Patient data will be pseudonymized at the local study centers and will be transferred in an anonymized fashion to the central database. Likewise, transmission of the core data set shared with the other studies within the network of the KfH Foundation for Preventive Medicine will be in anonymized form. All data management will be performed according to the principles of confidentiality and the regulations of national data protection laws (e.g., German Bundesdatenschutzgesetz [BDSG]).

Reference Data—Examinations in Healthy Controls

Reference values for cIMT measurements are available for subjects aged 10 to 20 years (9). For children aged 6 to 9 years, a reference cohort is currently being studied cross-sectionally.

No pediatric reference data for PWV and AI exist to date. Normative values will be obtained in approximately 1500 healthy children and adolescents aged 6 to 20 years. Healthy children will be enrolled from local schools in German, Turkish, Polish, Italian, and English cities.

For the analysis of 24-hour BP profiles, validated normative values are available from 1000 healthy European children examined with the same methodology (10).

Age-related data will be expressed in SD scores (SDS).

Statistical Procedures

The following working hypotheses will be tested:

(1) Patients with rapidly progressive CVD can be distinguished from patients with slow progression or stable cardiovascular function (rapid *versus* slow progressors).

This hypothesis will be addressed by comparing two subgroups of patients distinguished by the average change in cIMT. To that end, the observed intra-individual cIMT differences at the annual month examination time points will be averaged. In a pilot study, patients with progressive cardiovascular morbidity showed a mean increase in cIMT by 0.7 ± 0.5 SDS per year as compared with 0.0 ± 0.5 SDS change per year in stable patients (11). Making a conservative assumption of an average annualized change of 0.35 ± 1 SDS in the progressive *versus* 0.0 ± 1 SDS in the stable group, approximately 173 individuals per group will be required to detect a difference between groups as significant by two-sided *t* test. Accounting for a 15% cumulative dropout during 3 years of follow-up, 400 subjects will be required to test this hypothesis.

(2) Functional alterations of the vessels and myocardium precede structural alterations.

This hypothesis will be tested by correlating time-averaged functional parameters (PWV, systolic/diastolic myocardial

function) at the 0- and 12-month observations with time-averaged morphologic parameters (cIMT, LVMI) at the 24- and 36-month observations. Multiple linear regression analysis will be performed controlling for patient age, GFR, and time averaged BP. Inclusion of 376 patients will allow to explain a minimal variance in morphologic outcomes of 2.5% by functional parameters with 90% power and 1.5% alpha error.

(3) The progression of cardiovascular comorbidity is associated with the progression of CKD and its associated biochemical abnormalities.

Two statistical strategies will be used to identify anthropometric and biochemical predictors (biomarkers; Table 1) of progressive cardiovascular damage. Time-averaged means will be analyzed by two approaches. First, multiple linear regression analysis will be performed to assess independent relationships of the potential risk factors on vascular end points (mean change in PWV, cIMT, myocardial circumferential shortening, LVMI). Assuming that correction for the baseline value of each end point will account for 35% of total variance, inclusion of 540 patients will allow to detect independent effect sizes down to 2.5% variance at 80% statistical power if a maximum of 20 potential independent predictor variables are included in each single analysis. In a second approach, logistic regression analysis will be performed to express predictor effect sizes by odds ratios. Patients with progressor and nonprogressor status will be compared for vascular parameters. Assuming that the baseline probability of the progressor status is 0.33 and that regression of any particular independent variable of interest with the other covariates yields an R^2 of 0.15, inclusion of 488 patients will allow detection of odds ratios of 1.35 and greater at an error probability of 5% and a sensitivity of 80%.

(4) Individual common genetic variants affect the risk of progressive cardiovascular comorbidity in children with CKD.

(5) Individual common genetic variants affect the risk of renal failure progression in children with CKD.

A genome-wide association study will be performed to identify individual SNPs, haplotypes, or DNA copy number variations. Multiple equilibration disequilibrium testing will be performed in comparing cardiovascular progressor *versus* nonprogressor, and renal failure progressor *versus* nonprogressor status, respectively. The detectable relative risk of progression will be dependent on the marker allele frequency and the cohort size studied. If 500 patients are included, genetic markers associated with a relative risk of at least 1.45 will be detected with 80% power and an error probability of 5% if their allele frequency is at least 20% and those with a relative risk of at least 1.6 if allele frequency is 10%.

Determination of Sample Size

As detailed above, the estimated required number of patients to test working hypotheses 1 to 3 ranges between 376 and 540. Assuming a dropout of 15% within 3 years of follow-up, a minimum of 620 patients will be required.

This patient number will provide limited sensitivity to detect genetic markers of progressive cardiovascular lesions and renal failure. Therefore, it is planned to combine the 4C genotype data set with other pediatric CKD cohorts (The Effect of Strict

Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients [ESCAPE] study, North American Chronic Kidney Disease in Children [CKiD] study) to optimize statistical power. For testing of genetic markers of renal failure progression, combination with the available ESCAPE and CKiD cohorts will increase the sample size to 1500 subjects.

Ethical Aspects

The patient information and consent forms (translated into the national language) have been reviewed and approved by the local Institutional Review Boards in each participating institution.

Appropriate measures will be used to guarantee maximal data confidentiality. All patient-related clinical data will be pseudonymized locally. Blood samples for genetic testing will be double-coded. Neither the laboratories nor the central office are able to personally identify individual patients, and no investigator outside the central office will be able to correlate genetic results with clinical or laboratory data.

Discussion

Previous studies in children have shown that CKD-related risk factors are strongly associated with the prevalence and severity of cardiovascular changes.

In 156 children with CKD stage II to IV, the prevalence of left ventricular hypertrophy (LVH) was 35%, and age-corrected left ventricular mass was correlated with the degree of renal dysfunction (12). In the only prospective study performed so far in 31 CKD children (stage II to IV), 32% of patients developed LVH within 2 years (13). These findings confirm single-center experience reporting an LVH prevalence of 20% to 25% for CKD stage II to IV and 70% in CKD stage V patients (14). At attainment of end-stage renal disease and during dialysis treatment, 70% to 90% of pediatric patients present with LVH, which usually persists even after successful renal transplantation (15). LVH in children and young adults has been associated with male gender, obesity, and the severity of hyperparathyroidism and its treatment (16,17). Furthermore, 25% of 130

children with CKD stage II to IV presented with subclinical systolic dysfunction. This was associated with concentric LVH (18). In pediatric dialysis patients, systolic dysfunction can be often detected by use of tissue doppler imaging (19,20).

B-Mode ultrasound evaluation of the cIMT is an independent predictor of the risk of cardiovascular events. High-resolution ultrasound allows highly reproducible measurements of cIMT (21). Normative values for cIMT are available for adolescents (22). Increased cIMT has been described in young adults with childhood onset end-stage renal disease (23) and in children and adolescents with different stages of CKD, on dialysis and after renal transplantation (20,22). The cIMT was highest in dialysis patients, but found significantly increased in all stages of CKD and after transplantation (22). In this study, cIMT correlated with the mean past calcium-phosphate product, cumulative calcium-containing phosphate binder intake and the mean dose of calcitriol (22). Litwin *et al.* prospectively evaluated the evolution of cIMT in pediatric patients over 12 months and found rapid progression in CKD and dialysis patients and stabilization or partial regression in transplanted children (11).

M-Mode sonography allows measurement of local arterial stiffness, *e.g.*, expressed by the distensibility coefficient of the common carotid artery. The gold standard for assessment of systemic arterial stiffness is the measurement of carotid-femoral PWV (24). In addition, central pulse wave analysis allows the determination of the AI, an indirect measure of arterial stiffness (24). An increase of PWV and AI was found in pediatric patients on dialysis (25) and after transplantation (26). Mitsnefes *et al.* found significantly increased stiffness of the common carotid artery in 60 children with CKD and on dialysis. Arterial stiffness was correlated with serum calcium, phosphate, parathyroid hormone (PTH), and the cumulative dose of calcium-containing phosphate binders and calcitriol (27).

In several cross-sectional studies in young adults with childhood-onset CKD and children on dialysis, coronary calcifications were found in CT scans at a prevalence of 10% to 92% (23,28–31). In these studies, significant associations of coronary

Table 2. Key features of subclinical (asymptomatic) cardiovascular disease in children with CKD

1. Cardiomyopathy with LVH, often associated with diastolic and/or systolic dysfunction
2. Arteriopathy with
 - a. Morphological and functional anomalies of the conduit (carotid artery, cIMT) and muscular arteries (femoral artery, fIMT).
 - b. Functional anomalies: Decrease of post-ischemic vascular reactivity (endothelial dysfunction), increase of local (carotid artery), and systemic (PWV, AI) vascular stiffness.
 - c. Calcifications of the coronary arteries and heart valves.
3. Weak associations with classical risk factors (in patients with moderate CKD)
 - a. Hyperlipidemia.
 - b. Hypertension.
4. Robust associations with uremic risk factors (in patients with progressive or end-stage renal disease)
 - a. Alterations of the calcium/phosphate metabolism (serum levels of Ca, P, PTH).
 - b. Medical interventions.
 - i. Cumulative intake of calcium-containing phosphate binders.
 - ii. Active vitamin D preparations.

calcifications with the following factors were found: Age, duration of dialysis, markers of (chronic) infection (C-reactive protein [CRP], chlamydia antibodies), calcium/phosphate product, phosphate level, PTH level, and cumulative intake of calcium-containing phosphate binders and active vitamin D metabolites.

Thus, there is evidence for systemic CVD characterized by cardiomyopathy and arteriopathy in pediatric CKD patients (Table 2).

The 4C Study aims to characterize the most useful noninvasive technologies for cardiovascular monitoring, identify the pace at which CVD progresses, and detect the most relevant biochemical and genetic markers of progressive CVD and renal failure in children with CKD. The major challenge to meet these objectives is sample size. Because of the low incidence of CKD in childhood, a large encatchment area needs to be covered requiring multicenter and, in Europe, multinational cooperation. To meet this challenge, the 4C Study consortium will utilize and extend the infrastructure established in the ESCAPE trial, a recently concluded interventional study in children with CKD (32). For the genome-wide search for genetic risk markers of CKD progression, the 4C cohort will be combined with that of the ESCAPE trial and the cohort followed in the CKiD study (33) aiming at a total sample size of 1500 children.

Another challenge to be met by the 4C consortium is the absence or incomplete standardization and validation of most noninvasive cardiovascular monitoring technologies in children. In a joint effort, reference data for the vascular measurements will be obtained in a large representative sample of healthy children matched for age and region of origin.

Taken together, this study will investigate the extent and progression of cardiovascular morbidity using a broad spectrum of methods in the largest cohort of children and adolescents with CKD assembled to date. It is hoped that these data will allow individual risk assessment in pediatric patients and development of preventive strategies for the treatment of cardiovascular comorbidity.

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Disclosures

None.

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