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The French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study

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FULL REVIEW

ABSTRACT

Background. While much has been learned about the epidemiology and treatment of end-stage renal disease (ESRD) in the last 30 years, chronic kidney disease (CKD) before the end-stage has been less investigated. Not enough is known about factors associated with CKD progression and complications, as well as its transition to ESRD. We designed the CKD-renal epidemiology and information network (REIN) cohort to provide a research platform to address these key questions and to assess clinical practices and costs in patients with moderate or advanced CKD.

Methods. A total of 46 clinic sites and 4 renal care networks participate in the cohort. A stratified selection of clinic sites yields a sample that represents a diversity of settings, e.g. geographic region, and public versus for-profit and non-for-profit private clinics. In each site, 60–90 patients with CKD are enrolled at a routine clinic visit during a 12-month enrolment phase: 3600 total, including 1800 with Stage 3 and 1800 with Stage 4 CKD. Follow-up will continue for 5 years, including after initiation of renal replacement therapy. Data will be collected from medical records at inclusion and at yearly intervals, as well as from self-administered patient questionnaires and provider-level questionnaires. Patients will also be interviewed at baseline, and at 1, 3 and 5 years. Healthcare costs will also be determined. Blood and urine samples will be collected and stored for future studies on all patients at enrolment and at study end, and at 1 and 3 years in a subsample of 1200.

Conclusions. The CKD-REIN cohort will serve to improve our understanding of the biological, clinical and healthcare system determinants associated with CKD progression and adverse outcomes as well as of international variations in collaboration with the CKD Outcome and Practice Pattern Study (CKDopps). It will foster CKD epidemiology and outcomes research and provide evidence to improve the health and quality of life of patients with CKD and the performances of the healthcare system in this field. **Keywords:** biomarkers, chronic kidney disease, clinical practice, cohort, quality of life

INTRODUCTION

Chronic kidney disease (CKD), as defined since 2002 by the presence of kidney damage or reduced glomerular filtration rate (GFR), affects ∼10% of the adult population worldwide and more than one-third of the elderly [1–4]. A recent large meta-analysis of 46 general population, high risk and CKD cohorts, including more than 2 million participants, showed that both low estimated GFR (eGFR) and high albuminuria were associated with increased risk of all-cause mortality, cardiovascular disease and progression to end-stage renal disease (ESRD) regardless of age [5–7]. Despite the consistency of CKD-associated risk estimates across cohorts, one of the most striking epidemiological observations remains the contrast between the small geographic variation in CKD prevalence and the large variation in ESRD incidence, three times higher, for example, in the USA than in Europe [2]. Whether this results from differences in genetic or environment-related risk factors or clinical practice is unexplained.

ESRD is a major outcome of CKD, with an important effect on mortality, morbidity, quality of life and health resource utilization [8–10]. In France, the overall incidence of treated ESRD was 149 per million population (pmp) in 2011 and rose 7% since 2007, mainly due to population growth and ageing [11]. Advanced CKD, defined by an eGFR <30 mL/min/1.73 m^2, and the transition to ESRD constitute high clinical risk situations with substantial healthcare costs, but remain understudied. In 2010, 20% of all patients starting haemodialysis versus 5% of those starting peritoneal dialysis had no prior nephrology care [11]. A most concerning issue is the high proportion of emergency dialysis (∼30%) [12]. A greater understanding of individual, provider and healthcare system determinants is needed to reduce this risk.

The kidney plays a major role in the balance of multiple endogenous and exogenous compounds. CKD is associated with a set of metabolic [13, 14] and vascular complications [15–17] with a high risk of cardiovascular disease [5–7] as well as several other acute or chronic conditions, including acute kidney injury [18], infections [19], fractures [20], cancer [21], cognitive impairment [22] or sleep disorders [23], the determinants and mechanisms of which are not fully understood. Renal function decline also increases the risk for inappropriately high pharmacokinetic exposure to drugs cleared by the kidneys and severe adverse effects [24, 25]. Finally, quality of life and patient rating of healthcare remain under studied in early-stage CKD despite increasing recognition of the importance of patient-reported outcomes in clinical trials and public health [26–31]. Thus, studies are needed to increase knowledge aiming at improving the prevention of adverse outcomes in CKD. The identification of new predictive markers is also necessary to improve risk assessment in CKD. Several biomarkers emerging from experimental or epidemiological studies are promising [32], but further evidence is needed before they can be routinely used to predict outcomes. Prospective cohort studies on CKD are scarce [33] and only a few have biological samples and large sample size [34–36]. These studies primarily focus on the various pathophysiological aspects of CKD. But, because the causes of adverse outcomes in chronic diseases are multifactorial, it is worth considering potential interactions between a set of determinants including psycho-social, environmental, biological and genetic factors, as well as clinical practices and healthcare organization.

The Chronic Kidney Disease Outcomes and Practice Pattern Study (CKDopps), an international prospective nephrology clinic-based cohort conducted by Arbor Research Collaborative for Health (in the USA), was initiated to gather data about patients with advanced CKD (Stage 4) and study variations in outcomes and cost-effectiveness across a wide range of practices to identify those associated with the most favourable outcomes. To date, three countries are participating in this study, including Brazil, Germany [37] and France (with funding from the *Programme Hospitalier de Recherche Clinique 2010*). Additional participation, including the USA, is expected. The *Cohortes: Investissements d'avenir* programme was launched by the French government through the *Agence Nationale de la Recherche* to support large cohorts in order to foster epidemiology and outcome research in major public health domains. This provided a unique opportunity to set up the CKD-renal epidemiology and information network (REIN) cohort, a study with extensive objectives that include those of the international CKDopps programme.

Study objectives

The primary objective of the CKD-REIN cohort study is to develop a research platform to address key questions regarding various patient-level factors and biomarkers associated with CKD outcomes, and to assess clinical practices and healthcare system-level determinants of CKD outcomes. CKD-REIN will provide data, biological samples and long-term follow-up for a large cohort of patients with CKD Stage 3–4:

- To assess the associations of a set of psychosocial, environmental, biological and genetic factors, and their interactions with several renal and non-renal outcomes.
- To assess the value of new biomarkers to predict CKD progression and outcomes.
- To evaluate the associations of a set of provider practices regarding CKD management, healthcare organization and clinic services offered to CKD patients with end points such as survival, incident ESRD, hospital admissions, patient-reported outcomes and achievement of clinical practice guidelines, at both national and international (CKDopps) levels.
- To identify and quantify the net costs of different treatment practices and combine these with estimated practice effects on patient outcomes to provide estimates of incremental cost-effectiveness ratios, at both national and international levels.

A secondary objective aims at assessing the burden of nephrology-led CKD care through the yearly census of all patients with non-dialysis, non-transplanted CKD Stages 3–5 seen in participating nephrology clinics.

MATERIALS AND METHODS

Study organization

The CKD-REIN study is coordinated by the *Inserm* and *Université Paris-Sud* Centre for Epidemiology and Population Health, the database is managed by the *Agence de la Biomédecine* who also runs the REIN registry, and biological samples are centrally stored in the *Biobanque de Picardie*. A *partnership council* meets annually to assess study progress; a *steering committee* (SC) comprising the 12 study partners meets monthly and takes any decisions regarding the study; an international *scientific committee* advises the SC on study protocol and research works; an *industrial committee* comprising representatives of industrial partners and three SC members provides input from an industry perspective; an *ethic committee* advises the SC on any ethical aspects. The CKDopps SC chair is member of the CKD-REIN SC and three members of the CKD-REIN SC are members of the CKDopps SC.

Study design and participants

CKD-REIN is a clinical-based prospective cohort enrolling patients with CKD Stage 3–4 receiving nephrologist-led care. A key goal is to obtain a representative sample of 3600 patients, of whom 1800 have CKD stage 3 and 1800 stage 4. Study eligibility requires two measures of eGFR between 15 and <60 mL/min/1.73 m^2 at least 1 month apart without prior chronic dialysis or transplantation. Patients <18 years old or unable to give informed consent are excluded, as well as those who plan to move or decline participation.

Selection of clinical centres and recruitment goal

In order to describe actual CKD care at the national level and maximize variation in clinical practices and outcomes, we proceeded in two steps to select clinical settings. We first identified all of the 241 nephrology outpatient clinic settings which were classified by *department* and legal status: public, private-for-profit and private non-for-profit (Table 1). A total of 22 *departments* out of 95 located all over continental France were selected. We then included all clinic settings in seven *departments* which had four or less of them, and a sample in the others in order to obtain a representative sample with respect to legal status (Table 1). We also considered recruiting patients from *renal care networks*. These networks—a total of seven of which four are dedicated to non-end-stage CKD—were developed in order to improve the detection and secondary prevention of CKD by providing standardized monitoring, educational programmes and information to CKD patients and their physicians on a voluntary basis. It is worth while to evaluate their input in the context of this study [38]. The mean recruitment goal is 72 patients per centre (60–90), according to settings, and 150 for renal care networks.

Patient census and enrolment

For each participating clinic and renal care network, a census will be developed for all outpatients seen during the year-long enrolment phase with finalization at the end of the year. The goals of this census are to facilitate the identification of potentially eligible study patients, to characterize the underlying CKD Stage 3–5 population in participating clinics as well as to assess the representativeness of the study participants with respect to all potentially eligible outpatients. The census considers all outpatients seen over the period with nephrologist-confirmed CKD diagnosis and eGFR <60 mL/min/1.73 m^2. Patients with CKD Stage 5, with no prior dialysis or transplantation, are listed to enable the assessment of the prevalence of nephrology-led CKD care in the seven *departments* including all nephrology settings. Data elements collected for the clinic census include patient gender, age, places of birth and residence, diabetes status, type of CKD, eGFR and the number of visits at the clinic during the past year. Whenever possible, these data will be collected from available medical and/or administrative electronic database.

After obtaining informed consent, eligible patients with CKD Stage 3–4 are enrolled during a routine nephrology visit. Trained clinical research assistants (CRAs) interview the patients and collect data from their medical records. A nurse takes blood and urine for both routine biological measurements and biobank. Participants are also asked to fill out a self-administered questionnaire either at the nephrology clinic or at home.

Follow-up

All cohort participants will be assessed annually for at least 5 years, including after the start of renal replacement therapy. Each year, data will be drawn from both medical records and health insurance files and patients will be asked to report clinical events. Interviews, self-administered questionnaires and routine biological measurements will be repeated at year 1, 3 and 5. For those lost to follow-up, we will search the national REIN and death registries for ESRD, vital status and causes of death. Passive follow-up through national registries will also be applied to all eligible patients in order to validate cohort representativeness.

Data collection and routine laboratory measurements

Data collection instruments include patient-level and provider-level questionnaires addressing both CKD-REIN and CKDopps objectives. Main topics considered in patient-level

Table 1. Distribution of nephrology outpatient clinics by legal status in France and in the CKD-REIN cohort

Status	Public	Private non-for-profit	Private-for-profit	Total
All outpatient clinics	168 (70%)	24 (10%)	49 (20%)	241 (100%)
CKD-REIN clinical sites	30 (65%)	4 (9%)	12 (26%)	46 (100%)

questionnaires are presented in Table 2. It is worth noting that we are planning to collect a large number of sociodemographic, environmental and lifestyle data in the same way as in the Constances study to enable further comparisons with this large population-based cohort [39]. Several scales will be used to assess mental health [40], activities of daily living [41, 42] and family relationships [43]. Provider-level questionnaires will collect data about clinic characteristics, organization and staffing, patient education, clinical management of blood pressure, CKD complications and vascular access, as well as transition to ESRD and transplant evaluation. Whether or not patients and their provider participate in a renal care network will be recorded. We will also search the national health insurance database to assess resource utilization indicators at the patient level, e.g. hospitalizations, clinic visits, laboratory measurements and imaging examinations, and drug prescriptions. The *Etablissement français du Sang* will provide comprehensive data on blood transfusions. Biological markers recommended by the French Health Authorities for routine care of CKD will be systematically measured in all patients at baseline and follow-up visits (Table 3).

Study outcomes

CKD-REIN will follow up a number of renal and non-renal events. Renal events include progression to ESRD, treatment modality choice and timing of dialysis initiation, timing of conservative therapy if this option is chosen by the patient, timing of transplantation and wait-listing and episodes of AKI. Non-renal events include mortality and causes of death, cardiovascular disease (coronary heart disease, acute coronary syndrome, stroke, peripheral arterial disease, heart failure, dysrhythmia, sudden death, venous thromboembolism and pulmonary embolism), infections, fractures, cancer, cognitive impairment or sleep apnoea. Women health events including pregnancy outcomes, dysmenorrhoea, hormonal treatments and menopause will also be investigated. Quality of life will be assessed using validated adaptations of the 12-Item Short Form Survey (SF-12) and the Kidney Disease Quality of Life Instrument (KDQOL) [44]. Finally, adverse drug effects will be recorded from medical records and patient interviews, and hospitalizations from both medical records and health insurance files.

Table 2. Patient-level questionnaires and recorded data at baseline and/or follow-up

Questionnaires	Data
Baseline medical questionnaire	Demographics
	CKD history
	Cardiovascular and renal risk factors
	Medical history
	Kidney imaging (kidney size)
	Clinical and biological measurements prior to inclusion
Interval summary	Patient status: vital status, renal replacement therapy
	Number of visits
	Routine blood and urine laboratory measurements
	Clinical and anthropometric measurements
	Hospitalizations, acute kidney injury
	Imaging with contrast agents
	Transfusions; nutrition therapy; immunizations
	CKD care and preparation for ESRD and renal replacement therapy
Medications	Generic drug name; dosage; indication; date at start and end of treatment; adverse drug events
Dialysis access	Access type, localization, date created, date of failure if any, date of first use
Patient self-administered questionnaire	Quality of life instruments : SF 12, KDQOL-SF™
	Mental health (CES-D scale), activities of daily living, family relationships
	Global Physical Activity Questionnaire (GPAQ)
	Sleep, diet
	Social and demographic characteristics
	Medical expenses and health insurance
	Physician contacts, dietary and social services
	Kidney disease education and planning
	Satisfaction with care
	Women health
	Occupational history
Patient interview and examination	History of diabetes and hypertension, birth weight
	Smoking, alcohol and non-alcohol drinkings
	Adherence to treatments and adverse drug events
	Anthropometric measurements (see Table 3)
	Mini-Mental State Examination (MMSE)
Renal replacement therapy questionnaire[a]	Date at initiation and modality of renal replacement therapy
	Blood and urine laboratory measurements
	Clinical and anthropometric measurements
	Hospitalizations, transfusions
Death questionnaire	Date, place, underlying and contributing causes of death; conservative or palliative care before death

[a]RRT questionnaire recorded at follow-up, only.

Table 3. Study clinical and standard biological measurements

Type	Measurements
Anthropometry	Body weight and size
	Waist circumference, hip circumference
Clinical measures	Heart rate
	Sitting blood pressure
Blood parameters	Creatinine (enzymatic method)
	BUN
	Serum ionogram
	Albumin
	High-sensitivity CRP
	Calcium, phosphore, parathyroid hormone, 25-OH vitamin D
	Serum alkaline phosphatase
	Haemogram, haemoglobin, reticulocytes and percentage of hypochromic red blood cells
	Ferritin, serum iron, transferrin, transferrin saturation coefficient
	Fasting lipids
	Fasting glycaemia
	HbA1c
	Uric acid
24 h urine samples	Na, K, urea, protein, albumin, creatinine
Spot urine sample	Haematuria, leukocyturia

Sampling collection and storage

Fasting blood and second morning urine samples will be collected in all participants at enrolment and at study end, as well as at the 1- and 3-year follow-up in a subsample of 1200 patients. Serum, plasma, DNA and RNA will be stored at ultra-low temperature at the Biobanque de Picardie, an ISO 9001 and NFS 96900 certified biological resources centre.

Data entry and protection

The *Agence de la Biomedecine* maintains a national Information System for the management of the national transplant waiting list, the evaluation of transplant activities and the REIN registry. A web-based data collection system was developed for CKD-REIN using the same secured web portal and patient identification module. The use of a common patient identifier between CKD-REIN and the REIN registry will substantially facilitate the identification of ESRD events for patients lost to follow-up. The confidentiality, security and the integrity of data are covered by the *Agence de la Biomedecine* information system as it is a very sensitive issue for data regarding organ donation (secured portal, encryption, mirror copies of databases on servers located in another site).

Relevant quality control checks and queries will be executed at the national level by the CKD-REIN data manager and at the international level by Arbor Research. Data will be run through quality control programmes (e.g. meet range checks, units of measure, evaluation of non-response, etc.).

Statistical analyses and sample size considerations

Standard analyses will be carried out to describe patients and clinical practices, overall and by subgroups defined by age, gender and diabetes status. Multivariate regression models will be used to study the associations between patient characteristics, biomarkers, or clinical practices and the various study outcomes. We will systematically search for interactions between determinants and their impact on CKD outcomes, based on *a priori* hypotheses. In standard observational analyses to estimate treatment effects, the true effect may be distorted by indication bias. To lessen this bias, we will use a provider-based analytic approach, which is conceptually similar to instrumental variable analysis, to address indication bias; this methodology is commonly used in clinical studies such as the Dialysis Outcomes and Practice Pattern Study (DOPPS) [45, 46].

Regarding sample size, with 3600 patients, the minimum detectable hazard ratios for a time-to-event (e.g. survival) analysis comparing event rates from two equal groups with two-sided $\alpha = 0.05$, 80% power, an average follow-up of 5 years and 10% loss of follow-up time are 1.25, 1.18 and 1.13, for event rates of 0.05, 0.10 and 0.20/year, respectively. The event rates of 0.05 and 0.1/year are based on published estimates of mortality before ESRD in patients with CKD Stage 3 or 4, respectively [5]. ESRD rates may be higher than mortality rates, and composite ESRD or mortality may exceed 0.2/year [47, 48].

DISCUSSION

The CKD-REIN cohort will provide a research platform with a broad set of data and biological samples from patients with moderate or advanced CKD receiving nephrologist-led care to answer key questions regarding new risk assessment tools and best provider practices to improve patient outcomes. The most original aspects of the CKD-REIN study include the ability to conduct translational research of both type 1, *from bench to bedside*, and type 2, *from bedside to population*. Moreover, CKD-REIN addresses the objectives of the international CKDopps study and applies its design, which will contribute to developing an evidence base for the effective treatment of advanced CKD in real life in several countries and to the better understanding of determinants of geographic variation in ESRD incidence.

The CKD-REIN study is designed to investigate multiple CKD outcomes including mortality, CKD progression and ESRD, acute and chronic clinical events, as well as patient-centred outcomes. It will rely on several sources of information to improve identification of clinical events. The CKD-REIN study is also designed to investigate multiple determinants in relation to CKD outcomes, from genes to psychosocial and economical factors. A multidisciplinary approach was a prerequisite to receive funding by the *Cohorte: Investissement d'avenir* call for tender whose goal was to foster medical research by setting up large research platforms with biobanks. The CKD-REIN investigators have indeed expertise in various disciplines including clinical nephrology, epidemiology, bioinformatics and statistics, health economics, sample collection, biobanking, genomics and proteomics and basic sciences.

A major strength of the CKD-REIN study is that it is based on a nationally representative sample of patients, which will enable generalizability of our findings to the whole metropolitan French CKD patient population. It will complement both the national REIN registry [49], which collects data on all ESRD patients on renal replacement therapy, and the *Constances*

study [39], an ongoing population-based cohort including 200 000 adults aged 18–69 years selected at random from Health Screening Centres. *Constances* will enable the estimation of CKD prevalence, inform about the rates of nephrology referral and care for those diagnosed with CKD and, eventually, assess hospitalization, ESRD and mortality risks. It may also serve as a control population for CKD-REIN in the study of environmental or genetic factors. Altogether, these three databases will provide a comprehensive overview of CKD epidemiology and care in France from early detection to ESRD and beyond.

Transition to ESRD in advanced CKD is a major topic of interest for both the CKD-REIN and CKDopps studies. A most innovative aspect of the design is that patients will be closely followed up after the transition to ESRD across a wide variety of clinic settings. This will enable the identification of provider practices associated with better clinical outcomes and quality of life both before and after starting renal replacement therapy. Moreover, conservative management, also referred to as palliative care, will be carefully addressed in response to the growing concern over the past 10 years about alternatives to haemodialysis for the elderly with ESRD. Recent studies showing the high level of both regret for having started haemodialysis and subsequent withdrawal from haemodialysis suggest that this option may not meet all patients' needs, and that its harms may outweigh its benefits in some patients aged 75 years and older [50]. However, tools to assess the patient's preference and prognosis are needed to aid in decision-making on whether to proceed with dialysis or not for elderly patients with advanced CKD.

Major advances are to be expected from the CKD-REIN study and the international CKDopps study in the understanding of optimal clinical practices and healthcare organization in CKD. A major determinant of CKD outcomes is the ability of healthcare providers to interact and exchange patient information. Lack of coordination of care results in suboptimal use of nephroprotective therapy, suboptimal management of CKD complications and finally, high levels of emergency dialysis starts. Comparisons of clinical practices and modalities of interactions between physicians in CKD management across a variety of clinic settings, at both the national and international level, will enable the identification of those that would reduce emergency start, adverse CKD outcomes and improve access to wait-listing and transplantation. International comparisons will be particularly important to identify best treatment practices and care organization to improve efficiency and cost-effectiveness at the time of transition to ESRD.

The CKD-REIN study is facing a unique challenge in that it aims at providing an unbiased view of routine CKD care in a wide variety of settings, while collecting standardized data for the purpose of high level aetiological or translational research. This latter objective usually is carried out in a limited number of university hospitals with research infrastructure that facilitates biosample collection. To achieve these two goals concurrently, we selected a representative sample of nephrology clinic settings and patients are interviewed during routine visits. The only deviation from routine clinical care consists of measuring a set of blood and urine parameters as recommended by health authorities systematically four times in 5 years which should not strongly influence current practices. The *Etablissement français du Sang* network enables the collection of biological samples from all sites using its national infrastructure for blood donation, which guarantees high quality from sampling to final storage at the *Biobanque de Picardie*.

The CKD-REIN research platform can serve for ancillary studies and we will encourage innovative projects and broad use of data by external research groups to enhance the scientific output of the study. Its implementation will improve the understanding of the determinants associated with CKD progression and adverse outcomes as well as of international variations, and foster CKD epidemiology and outcome research. It will also provide evidence to improve the health and quality of life of patients with CKD and the performances of the healthcare system in this field.

AUTHORIZATIONS

All legal autorizations were obtained including those from the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS N° 12.360), the Commission nationale de l'informatique et des libertés (CNIL N° DR-2012-469) and from the Kremlin-Bicêtre Comité de protection des personnes (CPP N° ID RCB 2012-A00902-41). CKD-REIN biological collection is registered in the management application of the COnservation D' Eléments du COrps Humain (CODECOCH N° AC-2012-1624).

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CONFLICT OF INTEREST STATEMENT

None declared.

APPENDIX: CKD-REIN CLINICAL SITES AND INVESTIGATORS, BY REGION

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Renal care networks: TIRCEL (Pr M. Laville), NEPHROLOR (Pr M. Kessler), NEPHROLIM (Pr M. Essig) and RENIF (Dr X. Belenfant).

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FULL REVIEW

The dialysis scenario in patients with systemic lupus erythematosus

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ABSTRACT

Although prognosis of lupus nephritis has improved over time, a substantial amount of lupus patients still reach end-stage renal disease and require dialysis. Treatment of these patients can be challenging, since the disease poses a number of problems that can portend a poor prognosis, such as infections, lupus reactivations, vascular access thrombosis and cardiovascular complications. Consensus is lacking among investigators about the real incidence of these complications and related diagnosis and treatment. Moreover, the choice of the type of dialysis treatment and the overall prognosis are still a matter of debate. In this paper, we have reviewed the currently available literature in an attempt to answer the most controversial issues about the topic.**Keywords:** dialysis, ESRD, lupus, SLE

INTRODUCTION

The prognosis of lupus nephritis has considerably improved over time. In 1964 the seminal study of Pollak *et al.* [1] reported that only 20% of patients treated with high-dose