The chronic kidney disease outcomes and practice patterns study Brazil (CKDopps-Brazil): Design, data and methodology

Estudo dos desfechos de doença renal crônica e padrões da prática atual - Brasil (CKDopps-Brazil): Desenho, dados e metodologia

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Abstract

Introduction: *The chronic kidney disease outcomes and practice patterns study (CKDopps)* is an international observational, prospective, cohort study involving patients with chronic kidney disease (CKD) stages 3-5 [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, with a major focus upon care during the advanced CKD period (eGFR < 30 ml/min/1.73 m^2)]. During a 1-year enrollment period, each one of the 22 selected clinics will enroll up to 60 advanced CKD patients (eGFR < 30 ml/min/1.73 m^2 and not dialysis-dependent) and 20 earlier stage CKD patients (eGFR between 30-59 ml/min/1.73 m^2). Exclusion criteria: age < 18 years old, patients on chronic dialysis or prior kidney transplant. The study timeline include up to one year for enrollment of patients at each clinic starting in the end of 2013, followed by up to 2-3 years of patient follow-up with collection of detailed longitudinal patient-level data, annual clinic practice-level surveys, and patient surveys. Analyses will apply regression models to evaluate the contribution of patient-level and clinic practice-level factors to study outcomes, and utilize instrumental variable-type techniques when appropriate. **Conclusion:** Launching in 2013, CKDopps Brazil will study advanced CKD care in a random selection of nephrology clinics across Brazil to gain understanding of variation in care across the country, and as part of a multinational study to identify optimal treatment practices to slow kidney disease progression and improve outcomes during the transition period to end-stage kidney disease.

Keywords: clinical protocols; multicenter study; renal insufficiency, chronic; treatment outcome.

Resumo

Introdução: O Estudo de padrões da prática e desfechos das doenças renais crônicas (CKDopps) é um estudo internacional observacional, prospectivo, com uma coorte composta de pacientes com doenças renais crônicas (DRC) nos estágios 3-5 [taxa de filtração glomerular estimada (eGFR) < 60 ml/min/1,73 m^2, com um grande foco sobre o tratamento durante o período de doença renal crônica avançada (eGFR < 30 ml/min/1,73 m^2)]. Durante o período de recrutamento de participantes, de 1 ano, cada uma das 22 clínicas selecionadas inscreverá até 60 pacientes com DRC avançada (eGFR < 30 ml/min/1,73 m^2 e não dependente de diálise) e 20 pacientes com DRC em estágios anteriores (eGFR entre 30-59 ml/min/1,73 m^2). Os critérios de exclusão são: idade < 18 anos; pacientes em diálise crônica ou transplante de rim prévio. O cronograma de estudo inclui até um ano para a inscrição dos pacientes em cada clínica a partir do final de 2013, sendo então acompanhados por 2-3 anos, com coleta de dados longitudinais detalhados dos pacientes, pesquisas anuais dos níveis da prática na clínica e levantamentos de informação dos pacientes. As análises aplicarão modelos de regressão para avaliar a contribuição de fatores relacionados à clínica e aos próprios pacientes para estudar os desfechos, e utilizar técnicas do tipo: variável instrumental, quando apropriado. **Conclusão:** Lançado em 2013, o CKDopps-Brasil, avaliará o tratamento de DRC avançada em uma seleção aleatória de clínicas de nefrologia em todo o Brasil para entender como o tratamento varia em nosso país, e como parte de um estudo multinacional para identificar as práticas de tratamento ideal para retardar a progressão da doença renal e melhorar os desfechos durante o período de transição para a doença renal em estágio terminal.

Palavras-chave: estudo multicêntrico; insuficiência renal crônica; protocolos clínicos; resultado de tratamento.

Introduction

Chronic kidney disease (CKD) and the transition to advanced CKD (stage 5) increases risk of morbidity and mortality for patients as well as social and financial burdens and high costs for the health care systems in general.[1-4] However, especially in developing countries, scientific evidence is lacking. In Brazil, there are few population-based studies on CKD.[5-7]

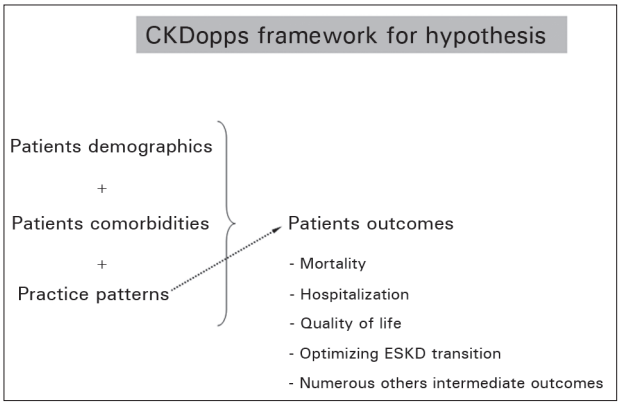
Actually, around one hundred thousand patients were on dialysis in Brazil, most part of them in hemodialysis. The estimated prevalence and incidence rates of end-stage CKD patients on maintenance dialysis were 483 and 100/million population, respectively. The estimated number of patients starting a dialysis program in 2010 was 18,972. The annual crude mortality rate was 17.9%.[7] Apart of these data, there are no substantial information concerning the impact of treatment options on survival, quality of life, delaying or non-indication of dialysis and treatment cost since earliest stages until end-stage CKD. Regarding early stages of CKD, according data from Brazilian Society of Nephrology (BSN), is estimated that in Brazil there are about 10 million of person with some degree of CKD. Considering that in Brazil (2009) 24.4% and 5.8% of the general population self reported as having systemic arterial hypertension and *diabetes mellitus*, respectively, seems reasonable to assume that this number of patients with some degree of kidney dysfunction are a realistic possibility.[8,9]

The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) is an international, prospective, observational cohort study of stages 3, 4, and 5 CKD patients [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, with a major focus upon care during the advanced CKD period (eGFR < 30 ml/min/1.73 m^2)].

The initial countries participating in CKDopps include Germany, France, Canada, United States of America, and Brazil, with others expected to join. Due to the variability in treatment approaches in CKD observed throughout the world, the international nature of the study can enhance the investigation and understanding of CKD practices in general.

CKDopps will produce detailed clinical and practice data that will serve as a research platform for understanding optimal practice in advanced CKD. The primary mission of CKDopps is to identify the links between the modifiable practices of CKD care and related patient outcomes, in an attempt to improve survival, burden of illness, and quality of life for these patients. To accomplish this goal, the hypotheses for the CKDopps study are (as depicted in Figure 1): broad hypotheses for CKDopps are that clinical outcomes vary among clinics even when accounting for patient characteristics; practice variation explains much of the difference in clinical outcomes; and that practices associated with optimal outcomes can be identified as a means to readily improve patient care.

Figure 1. CKDopps framework for hypothesis. ESKD, end-stage kidney disease.



CKDopps is coordinated by the *Arbor Research Collaborative for Health*,[10] a non-profit research organization that conducts studies in healthcare involving advance stage of CKD and organ failure. The Brazilian arm of this study (CKDopps-Brazil) will be coordinated by a committee of the Brazilian Society of Nephrology (BSN).

The main goals of the CKDopps-Brazil are:

1. To recruit and follow a randomly selected sample of CKD patients to represent the majority of CKD patients treated in nephrology clinics in Brazil.
2. To collect comprehensive, prospective, longitudinal data including numerous measures of patients characteristics (e.g., demographics, comorbidities, socioeconomic status, patient self-reported measures), clinical practices, laboratory measures, medication prescription, patient education, and preparation for end-stage kidney disease (ESKD).
3. To identify the associations between standards of clinical practice and important outcomes including all-cause and cause-specific mortality and hospitalization, CKD progression, and patient self-reported outcomes (e.g., quality of life, depression, life-style preferences).

4. To facilitate the generation of hypotheses involving the relationship between traditional risk factors and non-traditional risk factors with clinical outcomes.
5. To evaluate the impact of health policies, governmental regulations, clinical guidelines, and reimbursement policies upon the standards of clinical practice and outcomes.
6. To recommend successful and strategic treatments as preferential standards of practice.

This article provides an overview of the CKDopps-Brazil study design and methods, as well as its place within the multinational CKDopps program which has goal to generate evidence to improve care and optimize outcomes for CKD patients around the world.

Study design and methods

Study site selection

CKDopps-Brazil is a prospective cohort study of CKD stages 3, 4, and 5 patients treated at 22 randomly selected nephrology clinics in Brazil. Eligibility for study participation was pre-specified for the requirement that a clinic treat at least 40 advanced CKD patients (eGFR < 30 ml/min/1.73 m^2) in the prior year as indicate through contact with clinic medical directors. This specification was set based upon two study goals: (1) accurate data on at least 1,000 advanced CKD patients for the overall study to yield sufficient power for analyzing the primary study outcomes during the 2-3 years of study follow-up, and (2) collect data from a sufficiently large sample of patients at each clinic to provide stable estimates of numerous clinic-level practices.

In order to estimate the fraction of study eligible nephrology clinics in Brazil, the BSN surveyed a 20% random sample of all CKD clinics associated with the 683 dialysis units in Brazil, in March of 2011. This survey, translated into Portuguese, inquired about the distinct types of nephrology clinics, number of patients treated by CKD stage, regional differences, capacity for data collection, and capability to use a web-based data collection system for receiving and sending study data as is designed for CKDopps-Brazil. Survey results indicated that around 50% of dialysis units had a nephrologist-run CKD clinic associated with the dialysis unit, and approximately one-third of these nephrology CKD clinics treated at least 40 advanced CKD patients annually.

In addition, 90% of nephrology CKD clinics were indicated to be private clinics, with 10% described as university-run clinics. Based on this latter information, the CKDopps Brazil study was designed to be comprised of 85% private nephrology clinics and 15% university nephrology clinics to allow representation of practice in each of these two main care settings. In addition, the CKDopps Brazil study was designed to represent all 5 regions of Brazil in proportion to the fraction of study-eligible clinics in each region. The stratified random sampling method applied in CKDopps has allowed a sample of participating clinics to be obtained in which the geographic distribution of study clinics closely reflects that of all study eligible CKD clinics in Brazil (Table 1). Finally, the acceptance rate for clinic participation in CKDopps-Brazil has been excellent with 85% of randomly selected clinics agreeing to participate in the study.

Table 1 CKDopps Brazil sampling

Region	Total eligible CKD clinics	CKDopps selected clinics
Central-West	46 (8.9%)	2 (10.0%)
North	22 (4.3%)	1 (5.0%)
Northeast	94 (18.3%)	3 (15.0%)
South	116 (22.5%)	5 (25.0%)
Southeast	237 (46.0%)	11 (50.0%)
Total	515 (100.0%)	22 (100.0%)

CKD: Chronic kidney disease; sampling design was set for inclusion of 3 university-based clinics and 17 non-university CKD clinics.

Study timeline

The study timeline (Figure 2) depicts the design of the CKDopps-Brazil study to include up to one year for enrollment of study patients at each clinic starting in the end of 2013, followed by up to 2-3 years of longitudinal patient follow-up, with analysis of study data throughout the study and up to one year following the completion of study follow-up. Patient-level study questionnaires will be completed at baseline and at 6 month intervals during study follow-up, with some data captured as frequently as monthly occurrences (e.g., laboratory data when measured on a monthly basis for certain patients). A 6 week pilot study, realized in May and June 2013, was carried out at 2 selected study clinics to optimize the data collection procedures and study instructions prior to start of the full study in the end of 2013.

Figure 2. CKDopps-Brazil study timeline.

Study patient selection

In the CKDopps-Brazil study, up to 60 advanced CKD patients (eGFR < 30 ml/min/1.73 m^2 and not dialysis-dependent) and 20 earlier stage CKD patients (eGFR 30-59 ml/min/1.73 m^2) will be enrolled by each clinic during the first year of study participation. To be eligible for the study, CKD non-dialysis patients must be at least 18 years old and not previously receiving a kidney transplant. The study is designed as a period prevalent cohort study with no replacement of patients who depart during follow-up. To minimize selection bias, patients will be approached for study participation and consent in the order of their first scheduled visit to the study clinic site during the 1 year enrollment period. Routine patient clinical data and clinic-level surveys will be collected as described below. All patients will be asked to complete a "patient questionnaire" once each year beginning at the time of study entry. However, study participants can allow their health-related information to be used for the CKDopps even if the patient does not wish to complete the patient questionnaire or skips a portion.

Informed Consent & protection of research subjects

Treatment of patients will not be affected by their participation in the CKDopps, and there will be no treatment intervention involved in this study. Data collection will be done anonymously with a high degree of confidentiality and security, as has been demonstrated throughout more than 16 years of the international DOPPS study. Patient participation occurs only after a patient has provided informed consent to participate in the study. Consent forms for the study will be those approved for use in CKDopps by the Ethics Committee with all study documentation translated into Portuguese. The CKDopps-Brazil study was approved by the Ethics Committee on Research at *Pontifícia Universidade Católica do Paraná - PUC-PR, Brasil* (CAAE: 14922513.0.1001.0020 - Document number: 256.525). All documentation of the study is translated into Portuguese.

Study data

CKDopps will collect patient and clinic-level data using instruments and protocols that are being applied by all the countries participating in the international CKDopps initiative. CKDopps is strictly an observational study of how patients are cared for as part of routine CKD practice. Thus, CKDopps is not an interventional study. For each clinic, a coordinator (clinic nurse or physician) is designated to collect the data for the study. Patient-level clinical data are collected in the study using the secure DOPPSLink web-based data collection system developed for CKDopps by Arbor Research Collaborative for Health with access only by authorized study-related personnel. DOPPSLink provides real-time data collection and quality checking, as well as study management utilities.

Following is a description of the questionnaires and data collected in the CKDopps-Brazil study.

Patient-level clinical data

Clinic Census - The census will be completed by the study coordinator using DoppsLink. The clinics will register information on all CKD patients that have a scheduled visit and are currently being treated at the clinic. Patients with eGFR < 60 ml/min/1.73 m^2 will be approached for inclusion in the study in order of scheduled visit. The clinic will continue to add patients to the census until reaching 80 enrolled study patients or until the end of 12 months, whichever occurs first. Basic information will be reported for each patient listed on the Clinic Census including age, sex, race, diabetes status, and most recent serum creatinine and eGFR level at the time of listing. In addition, for each of the 80 study patients participating in the study, reasons and date of study departure are captured.

Medical Questionnaire - This questionnaire is completed once at study entry for each study patient providing the following types of data: medical history (e.g., comorbidities), kidney disease history, prior kidney imaging study results (biopsies), prior serum creatinine, eGFR, hemoglobin, and blood pressure levels, and prior urinalysis results (protein, albumin, creatinine, sodium, 24-hour volume).

Interval Summary and Death Detail Form - used for longitudinal collection of specific patient data from the start of the study and every 6 months until the patient discontinues treatment at the study clinic. For patients who depart from the study, the living status of patients is captured up to 6 months following study departure along with reporting of date and causes of death during this time period. This living status reporting includes 6 months of follow-up after transition to chronic dialysis. Table 2 lists the

types of longitudinal data collected with the Interval Summary and Death Detail Form.

Table 2 The types of longitudinal data collected with the interval summary and death detail form

Clinical outcomes
- Death (date and death causes); - Hospitalization and outpatient visits (diagnoses and procedures); - Acute kidney injury episodes and acute dialysis; - Initiation of chronic dialysis; - Kidney transplantation and wait-listing.
Other data
- Frequency of clinic visits; - Blood and urine laboratory data; - Blood transfusions; - Blood pressure, heart rate, weight measurements; - Nutritional therapy; - Immunizations; - Medication use and dosage; - Dialysis access placement and other pre-ESKD care; - CKD and pre-ESKD education; - Type of health insurance; - Use of palliative/hospice care.

ESKD: End-stage kidney disease; CKD: Chronic kidney disease.

Patient self-reported data

Patient Questionnaire - Collected at study entry and annually thereafter using a questionnaire completed by patients and designed to obtain responses regarding the patients' quality of life, satisfaction, and other aspects of treatment. The types of data collected include: the kidney disease quality of life (KDQoL) instrument, CESD depression instrument, activities of daily living, diabetes and blood pressure management, CKD and pre-ESRD education, physical activity level, satisfaction with care, out-of-pocket expenses, frequency of yearly contact with different care specialists, and dietary and medication adherence.

Nephrology clinic-level data

Medical Director Survey and Nephrologist Survey - Questionnaires completed by the clinic medical director and treating nephrologists, respectively; designed for the collection of detailed information regarding the clinic's standards of practice, targets, and viewpoints on topics areas as shown in Table 3.

Data validation and analysis

The data will be validated upon receipt by the data control center, utilizing quality control programs which include verification of form completion, units of measure, non-responses, range and date checks, etc. Questions generated during this process of quality control are brought to the attention to the individuals responsible for primary data collection for verification of specific data. Once the quality control process is complete, the standardized analytic files are created for analysis of study data.

Table 3 Facility-level data collection content

Anemia and iron therapy; dietitian and nutrition practices; palliative/hospice care services; antihypertensive therapy and blood pressure management; clinic characteristics; transplant wait-listing; planning living donor-related transplantation; cardiovascular disease management; health care maintenance; quality assurance and improvement practices; diabetes management; hospital and outpatient practices; scheduling practices; continuing education policies/practice; immunization practice; social services practices; CKD and pre-ESKD patient education; information systems; physician and nurse practices; preparation/timing chronic dialysis initiation; insurance policies and vascular access or PD catheter creation.

CKD: Chronic kidney disease; ESKD: End-stage kidney disease; PD: Peritoneal dialysis.

Analysis methods

Associations between outcomes and indicators of practice and treatments will be analyzed both at the patient level, and when possible at the clinic level. Modeling approaches to be applied include: Poisson models (repeated event count), logistic regression, proportional risk hazard ratios (such as Cox survival regression in modeling time to death, hospitalization, or other events), log-linear model (cost analysis). Corrections for demographic characteristics and comorbidity differences will be applied. Models of repeated measures during the treatment period (time-dependent co-variable) will be applied when of interest for analysis of changes over time. Regression and hierarchal analyses will be performed so as to simultaneously control for patient and clinic-level factors and in particular to account for facility clustering effects.

Primary analyses of standards of practice will focus upon practice summaries from the dialysis clinics (for example, percentage of patients in a treatment category) through application of instrumental variable methodologies as a means minimize treatment-by-indication biases. Clinical outcomes typically will be based on the "patient" level outcome in order to maximize statistical

power and avoid use of ecologic-type analyses which are prone to confounding at a group variable level.

All analyses will attempt to identify potential confounding factors, and diagnostic tools will be used to evaluate quality and appropriateness of models according to accepted statistical practices. The majority of the analyses will be repeated using different levels of adjustments in order to enhance clinical comprehension and evaluate stability of the findings.

Study governance

The Brazilian arm of this study (CKDopps-Brazil) will be coordinated by a steering committee of the Brazilian Society of Nephrology (BSN), whose members are: Dr. Rodrigo Bueno de Oliveira, Dr. Ricardo Sesso, Dr. Jocemir Ronaldo Lugon, Dr. Antonio Alberto Lopes and Dr. Roberto Pecoits-Filho. Darlene Medeiros and Ludimila Guedim de Campos are site Coordinator for CKDopps in Brazil.

Data use and sharing

CKDopps is intended broadly to be a resource for the nephrology community to help inform and improve patient care and outcomes. Collaborative work, in the form of ancillary data collection or analyses that include external investigators, is encouraged. Requests for research collaboration, whether related to CKDopps in Brazil or internationally, should be submitted by external investigators for review by the CKDopps Steering Committee and Brazilian investigators.

Conclusion

Launching in 2013, CKDopps Brazil will study advanced CKD care in a random selection of nephrology clinics across Brazil to gain understanding of variation in care across the country, and as part of a multinational study to identify optimal treatment practices to slow kidney disease progression and improve outcomes during the transition period to end-stage kidney disease.

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