International Journal of Cardiology 202 (2016) 657–665

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Magnitude of rate of change in kidney function and future risk of cardiovascular events

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ARTICLE INFO

*Article history:*
Received 15 August 2015
Accepted 24 September 2015
Available online 28 September 2015

*Keywords:*
Rate of change
Magnitude
Kidney function
Stroke
Hurt failure
Myocardial infarction

ABSTRACT

*Background:* Using a community-based cohort we sought to investigate the association between change in estimated glomerular filtration rate (eGFR) and risk of incident cardiovascular disease including congestive heart failure (CHF), acute myocardial infarction (AMI), and stroke.

*Methods:* We identified 479,126 adults without a history of cardiovascular disease who had at least 3 outpatient eGFR measurements over a 4 year period in Alberta, Canada. Change in eGFR was estimated as the absolute annual rate of change (categorized as ≤−5, −4, −3, −2, −1, 0, 1, 2, 3, 4, and ≥5 mL/min/1.73 $m^2$/year). In a sensitivity analysis we also estimated change as the annual percentage change (categorized as ≤−7, −6 to −5, −4 to −3, −2 to −1, 0, 1 to 2, 3 to 4, 5 to 6, and ≥7%/year). The adjusted risk of incident CHF, AMI, and stroke associated with each category of change in eGFR was estimated, using no change in eGFR as the reference,

*Results:* There were 2622 (0.6%) CHF, 3463 (0.7%) AMI, and 2768 (0.6%) stroke events over a median follow-up of 2.5 years. Compared to participants with stable eGFR, those with the greatest decline (≤−5 mL/min/1.73 $m^2$/year) had more than a two-fold increased risk of CHF (HR 2.57; 95% CI: 2.28 to 2.89). Risk for AMI and stroke was increased by 31% and 29%, respectively. After adjusting for the last eGFR at the end of the accrual period, the observed association remained significantly higher for CHF but diminished for AMI and stroke. A similar pattern was observed when change in eGFR was quantified as annual percentage change.

*Conclusion:* In this large community-based cohort, we observed that a declining eGFR was associated with an increased risk of CHF, AMI, and stroke. However, when the risk of CVD events was adjusted for the last eGFR measurement, decline in eGFR per se was no longer associated with increased risk of AMI or stroke, and the association with CHF remained significant but was attenuated. These results demonstrate the importance of monitoring change in eGFR over time to improve cardiovascular risk prognostication.



## 1. Introduction

Chronic kidney disease (CKD) is a major public health problem worldwide affecting 10–16% of the adult population. Studies have demonstrated a graded increased risk of cardiovascular disease (CVD) events with worsening CKD, in both general and high-risk populations [1–7]. However, these reports have primarily considered kidney function at one point in time (the baseline), without considering how the change in kidney function over time influences the risk of future adverse outcomes. Based on the premise that the dynamics of change in kidney function using repeated kidney function measurements might contribute additional prognostic information beyond a single measurement, the association between change in kidney function over time and adverse outcomes has been evaluated in a few population-based studies [8–14]. However, only a few of them [8,13,14] have reported on the association between the changes in kidney function over time with risk of CVD, and are limited by their relatively small study size.

Using a population-based cohort of individuals receiving routine clinical care in a single Canadian province, we investigated the association between change in kidney function over time and risk of specific CVD events: congestive heart failure (CHF), acute myocardial infarction

*Abbreviations:* CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; CHF, congestive heart failure; AMI, acute myocardial infarction; ACR, albumin: creatinine ratio; AKDN, Alberta Kidney Disease Network.

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http://dx.doi.org/10.1016/j.ijcard.2015.09.090
0167-5273/

(AMI), and stroke. We explored change in kidney function using two indices; namely the absolute annual rate of change and the annual percentage change in estimated glomerular filtration rate (eGFR) of the study participants.

## 2. Methods

### 2.1. Design, setting, population, and data sources

We did a population-based cohort study of all adults aged 18 years or more in Alberta, Canada who had at least three outpatient serum creatinine measurements spanning a period of four calendar years (Fig. 1), using the data repository of the Alberta Kidney Disease Network (AKDN) [15] to define the cohort. The cohort accrual period was from 1 May 2002 to 31 December 2007, with follow-up extending to 31 March 2009. Patients receiving chronic dialysis or a kidney transplant on or before cohort entry were excluded. Among the 1,818,381 patients with at least one outpatient serum creatinine measurement, there were 529,954 participants for whom at least three or more measurements were available over a four-year period. We further excluded individuals with a history of CVD events, including CHF, AMI, and stroke, before the start of follow-up, as well as those with a baseline eGFR < 15 mL/min/1.73 $m^2$. The final study cohort consisted of 479,126 participants (Fig. 2).

### 2.2. Change in kidney function

We used the CKD-EPI equation to estimate the glomerular filtration rate (eGFR) [16]. Change in eGFR over time was estimated using all available outpatient eGFR measurements for each patient during the measurement accumulation period. The primary method we used to describe change in eGFR was the absolute annual rate of change, which was calculated by fitting a least-squares regression to all measurements for each patient [10,11], where the slope of the regression line describes the absolute rate of change for eGFR over time. The absolute annual rate of change in eGFR was categorized as ≤−5, −4, −3, −2, −1, 0, 1, 2, 3, 4, and ≥5 ml/min per 1.73 $m^2$ per year.

In sensitivity analysis, we used the percentage change in eGFR as an alternate way to define the change in eGFR over time. Percentage change in eGFR was calculated assuming a linear change on the log scale, consistent with prior work [8,11]. The annual percentage change in eGFR was categorized as ≤−7, −6 to −5, −4 to −3, −2 to −1, 0, 1 to 2, 3 to 4, 5 to 6, and ≥7%/year.

### 2.3. Covariates

Using the Alberta provincial health ministry administrative data sources, we determined the sociodemographic characteristics of the study participants. First Nations status was determined using the Alberta Health registry file. Although it was not possible to identify other race/ethnic groups, over 85% of the Alberta population is Caucasian [17]. Socioeconomic status was categorized based on the annual adjusted taxable family income based on Government of Alberta health care insurance records; high income (≥CAD 39,250), low income (<CAD 39,250), low income with subsidy (social assistance), and pensioners (≥65 years of age) [18]. Diabetes mellitus and hypertension were identified using validated algorithms from hospital discharge records and physician claims [19,20]. Other comorbid conditions based on the Deyo classification of Charlson comorbidities were identified from the physician claims and hospitalization records using validated ICD-9-CM and ICD-10 coding algorithms [21]. Proteinuria was estimated by urine albumin: creatinine ratio (ACR) or urine dipstick based on outpatient random spot urine measurements. Proteinuria was categorized as normal, mild, heavy, or unmeasured based on ACR [normal (ACR <30 mg/g), mild (ACR 30–300 mg/g) or heavy (ACR >300 mg/g)] or urine dipstick [(urine dipstick negative); mild (urine dipstick trace or 1+) or heavy (urine dipstick 2+)], as previously described [7,22].

Patients' demographics and comorbidities that have potential to change over time were measured at two time points. Covariates were first measured at the time point of the first eGFR measurement and the second time the covariates were measured was at the time of last eGFR measurement (Fig. 1).

### 2.4. Outcome ascertainment

Participants were followed from the date of the last eGFR measurement until study end (31st March 2009) ensuring at least one-year of follow-up for all study participants. Incident cases of CHF, AMI, and stroke were identified from the Alberta Health hospitalization and physician claims databases [15] based on validated algorithms [23–25].

### 2.5. Statistical analyses

Adjusted rates of CHF, AMI and stroke, expressed per 10,000 person-years, for each group of change in kidney function were calculated using Poisson regression. Analyses were adjusted for the sociodemographic variables, baseline eGFR, proteinuria and covariates as in Table 1. We considered two perspectives regarding adjustment for the covariates (including eGFR) — adjusting for the covariates extracted at the time point of the first eGFR measurement, and adjusting for the covariates extracted at the time point of the last eGFR measurement (Fig. 1). Adjusted rates were estimated separately for first and last eGFR measurement perspective. Cox proportional hazards models were used to estimate the adjusted risk of each of the CVD outcomes associated with each group of change in kidney function, with stable kidney function (0 ml/min per 1.73 $m^2$ per year for the absolute rate of change and 0%/year for percentage change) serving as the reference. Hazard ratios were also estimated separately after adjusting for first (baseline) and last eGFR measurement at the corresponding time point. The proportional hazards assumption was tested and met. Participants were censored at study end (March 31, 2009) if they were still at risk or at an earlier date if they experienced the event of interest, death or left the province.

We did several subgroup analyses to test the robustness of our results. We performed separate analysis for men and women. We also stratified participants into age <65 and ≥65 years. All analyses were performed using separate models adjusting for the covariates measure at either the first and last eGFR measurement. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC), and STATA version 12.0 (STATA Corp., College Station, TX).

### 2.6. Role of the funding source

The sponsor had no role in the design, data collection, data analysis, interpretation, writing of the report, or decision to submit the paper for publication. The institutional review board of the University of Calgary approved the study and granted waiver of patient consent.

## 3. Results

The distribution of annual rate of change appeared normal and centered near the origin (Fig. 3). The mean annualized absolute rate of

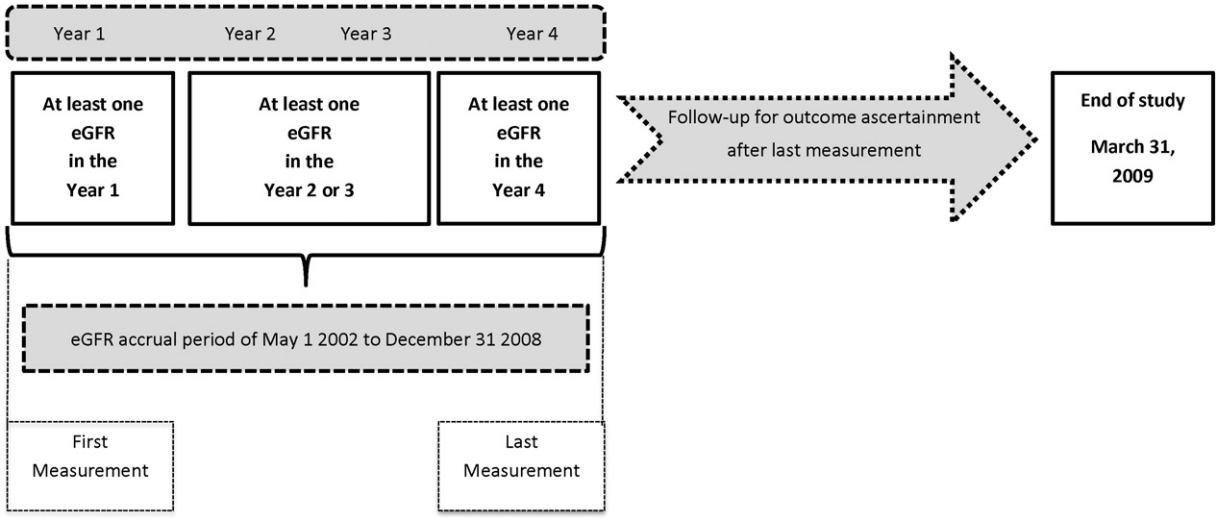


**Fig. 1.** Outline of cohort criteria.