Time-Updated Changes in Estimated GFR and Proteinuria and Major Adverse Cardiac Events: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

Jordana B. Cohen, Wei Yang, Liang Li, Xiaoming Zhang, Zihe Zheng, Paula Orlandi, Nisha Bansal, Rajat Deo, James P. Lash, Mahboob Rahman, Jiang He, Tariq Shafi, Jing Chen, Debbie L. Cohen, Kunihiro Matsushita, Michael G. Shlipak, Myles Wolf, Alan S. Go, and Harold I. Feldman, on behalf of the CRIC Study Investigators

Rationale & Objective: Evaluating repeated measures of estimated glomerular filtration rate (eGFR) and urinary protein-creatinine ratio (UPCR) over time may enhance our ability to understand the association between changes in kidney parameters and cardiovascular disease risk.

Study Design: Prospective cohort study.

Setting & Participants: Annual visit data from 2,438 participants in the Chronic Renal Insufficiency Cohort (CRIC).

Exposures: Average and slope of eGFR and UPCR in time-updated, 1-year exposure windows.

Outcomes: Incident heart failure, atherosclerotic cardiovascular disease events, death, and a composite of incident heart failure, atherosclerotic cardiovascular disease events, and death.

Analytical Approach: A landmark analysis, a dynamic approach to survival modeling that leverages longitudinal, iterative profiles of laboratory and clinical information to assess the time-updated 3-year risk of adverse cardiovascular outcomes.

Results: Adjusting for baseline and time-updated covariates, every standard deviation lower mean eGFR (19 mL/min/1.73 m²) and declining slope of eGFR (8 mL/min/1.73 m² per year) were independently associated with higher risks of heart failure (hazard ratios [HRs] of 1.82 [95% CI, 1.39-2.44] and 1.28 [95% CI, 1.12-1.45], respectively) and the composite outcome (HRs of 1.32 [95% CI, 1.11-1.54] and 1.11 [95% CI, 1.03-1.20], respectively). Every standard deviation higher mean UPCR (136 mg/g) and increasing UPCR (240 mg/g per year) were also independently associated with higher risks of heart failure (HRs of 1.58 [95% CI, 1.28-1.97] and 1.20 [95% CI, 1.10-1.29], respectively) and the composite outcome (HRs of 1.33 [95% CI, 1.17-1.50] and 1.12 [95% CI, 1.06-1.18], respectively).

Limitations: Limited generalizability of annual eGFR and UPCR assessments; several biomarkers for cardiovascular disease risk were not available annually.

Conclusions: Using the landmark approach to account for time-updated patterns of kidney function, average and slope of eGFR and proteinuria were independently associated with 3-year cardiovascular risk. Short-term changes in kidney function provide information about cardiovascular risk incremental to level of kidney function, representing possible opportunities for more effective management of patients with chronic kidney disease.
The investigation conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by institutional review boards at all participating centers, and all participants provided written informed consent.

Main Exposures

The primary exposures were time-updated eGFR and proteinuria. The eGFR was calculated at each study visit using the CRIC GFR estimating equation, which incorporates serum creatinine, cystatin C, age, sex, and race. Serum creatinine was measured by an enzymatic method from Ortho Clinical Diagnostics through October 2008 and by the Jaffe method from Beckman Coulter after October 2008; all creatinine values were standardized to isotope-dilution mass spectrometry–traceable values. Cystatin C was measured using a particle-enhanced immunephelometric assay. Proteinuria was determined using UPCR from 24-hour and spot urine specimens.

Baseline Covariates

Fixed baseline characteristics were sex, race/ethnicity, and education level. A medical history questionnaire was administered to all CRIC participants that obtained information on sociodemographic characteristics. Self-reported race/ethnicity was categorized as non-Hispanic white, non-Hispanic Black, Hispanic, or other.

Sensitivity analyses were adjusted for baseline total cholesterol, high-density lipoprotein, and fibroblast growth factor 23 (FGF-23). These values often change over time, but were available only at baseline and were not measured in all participants. Total cholesterol and high-density lipoprotein were measured using standard assays. FGF-23 was measured in duplicate using a second-generation C-terminal assay (Immutopics).

Time-Updated Covariates

Time-updated covariates included in the analyses were age, smoking status, alcohol use, hypertensive status, diabetes status, systolic blood pressure (BP), diastolic BP, heart rate, body mass index (BMI), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and serum albumin, hemoglobin, and bicarbonate levels. Smoking status was categorized as current smoker, past smoker, or never a smoker. Hypertension was defined as mean BP ≥140/90 mm Hg or self-reported antihypertensive medication use. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, or self-reported hypoglycemic medication use. At every annual visit, 3 seated BP measurements were obtained by trained staff following ≥5 minutes of rest and were averaged. Anthropometric measurements were obtained using standardized protocols at each visit. Anti-hypertensive medication use was determined by self-reported medications for the 30 days preceding annual study visits. Serum albumin, hemoglobin, and bicarbonate levels were measured using standard assays.

Methods

Study Design and Population

The CRIC Study is an ongoing multicenter observational cohort study of 3,939 individuals with CKD who were enrolled between June 2003 and August 2008 at 7 US clinical centers. Study participants are followed at annual clinic visits. The study design and baseline participant characteristics have been previously described. In brief, participants were eligible for enrollment if they were aged 21–44 years with an eGFR of 20–70 mL/min/1.73 m², aged 45–64 years with an eGFR of 20–60 mL/min/1.73 m², or aged 65–74 with an eGFR of 20–50 mL/min/1.73 m². Excluded were individuals who had previously received dialysis for at least 1 month, had a prior kidney transplant, required immunosuppression for the treatment of glomerulonephritis, or had a diagnosis of cirrhosis, polycystic kidney disease, or severe HF (defined as New York Heart Association Class III or IV).

For the present study, we excluded participants with any history of HF or ASCVD at the time of enrollment or in whom any of the outcome events developed before the end of the first exposure window.

Plain-Language Summary

Prior studies evaluating how markers of kidney function (estimated glomerular filtration rate [eGFR] and proteinuria) relate to heart disease risk have often been limited by the use of kidney function measurements from only 1 or 2 time points. Using data from 2,438 participants in the CRIC Study, we evaluated if repeated values of eGFR and proteinuria over time improved the understanding of how changes in kidney function are associated with the risk of developing heart disease. We observed that worsening 1-year average and slope of eGFR and proteinuria, captured repeatedly over time, were each associated with an increased 3-year risk of heart disease. Thus, short-term changes in kidney function provide useful information about heart disease risk and represent possible opportunities for better, targeted management of patients with chronic kidney disease.
Outcomes and Censoring Events

We evaluated cause-specific risk of incident HF hospitalization, ASCVD events (defined as myocardial infarction, coronary revascularization, stroke, or peripheral artery disease), all-cause death, and a composite of all of these events. Participants were censored at the time of kidney failure requiring kidney replacement therapy (defined as receipt of maintenance dialysis or kidney transplant), their last study visit, or death when it was not the outcome of interest. HF hospitalizations and ASCVD events were identified by asking study participants biannually if they were hospitalized and by reviewing electronic health records. Deaths were ascertained from next of kin, death certificates, obituaries, reviews of hospital records, and the Social Security Death Master File. At least 2 study physicians reviewed all events and deaths using medical records and determined the likelihood of events based on modified clinical Framingham criteria. Definite and probable events were considered outcome events for the present analyses. Outcomes were ascertained from study entry through January 2018.

Statistical Analyses

We employed the landmark method to examine the longitudinal profile of eGFR and UPCR with regard to each of the adverse cardiac outcomes. The landmark approach applies statistical modeling to evaluate associations of variables measured at or before a particular time point with outcomes that occurred after that time point. In our analyses, the exposure and outcome windows were defined over fixed durations of time and were repeated successively until the end of follow-up. We evaluated the changing patterns of eGFR and UPCR across 2 annual study visits (ie, 1-year exposure windows; Fig 1). Follow-up time started at the end of each exposure window. Each participant could have several exposure windows contributing to the model, depending on their duration of follow-up. Robust variance estimation was used to account for repeated measures within individuals. Within each exposure window, we estimated the slope of eGFR and UPCR using ordinary least squares. In addition to the slope, we considered using the mean exposure (evaluated at the middle of the exposure window using ordinary least squares) or its most recent value within the window. We assessed for collinearity between the mean and slope and the most recent value and slope of eGFR and UPCR. In view of the collinearity between the most recent value and slope for eGFR and UPCR (Table S1), we used the mean exposure and slope as the primary method of characterizing the exposure history. We examined the associations of each standard deviation (SD) difference in the average and slope of eGFR and UPCR with clinical outcomes within 3 years following the exposure window using Cox proportional hazards regression. Individuals were censored at the time of death (when it was not the event of interest), loss to follow-up, or the end of the outcome window. Hazard ratios (HRs) were averaged over the duration of follow-up.

For each outcome, we evaluated the following models: (1) simultaneous adjustment of eGFR average and slope, (2) simultaneous adjustment of log-transformed UPCR average and slope, (3) simultaneous adjustment of eGFR and log-transformed UPCR average and slope plus adjustment for all covariates, and (4) simultaneous adjustment of quartiles of eGFR and UPCR average and slope plus adjustment for all covariates. The results of the eGFR

![Figure 1. Landmark approach to time-dated analyses of average and change in estimated glomerular filtration rate (eGFR). These images depict how 3 hypothetical participants’ eGFR values would be incorporated into models evaluating time-updated 1-year exposure windows with 3-year outcomes. The gray box represents the exposure window. The solid vertical line represents the maximum time of the outcome and censoring. The solid circles represent the time of eGFR assessment for each participant. (Urinary protein-creatinine ratio was assessed at the same time points and was also subjected to landmark analysis.) Participant 1 experienced an acute cardiovascular event between years 5 and 6 of follow-up. Participant 3 experienced an acute cardiovascular event between years 4 and 5 of follow-up.](image-url)
analyses in models 1-3 are reported as inverse HRs to maintain comparable directionality with UPCR. Baseline and time-updated covariates were selected a priori using a knowledge-driven approach based on known associations with major adverse cardiac events\textsuperscript{3,22,24} and ready availability in routine clinical care. Time-updated covariates were included as the average value of the covariate during each exposure window.

Sensitivity analyses compared the results (1) using 2-year exposure windows (ie, using data from 3 annual study visits; depicted in Fig S1) and (2) evaluating 1-year end points. We also assessed for an interaction between average and slope of eGFR and between landmark time and each of the exposure parameters.

Results

Cohort Characteristics

Of the 3,939 CRIC Study participants, we excluded 1,501 with prior CVD events. The remaining 2,438 participants were included in the analyses. Participants had a mean age of 57 ± 12 (SD) years; 48% were female, 39% were non-Hispanic Black, and 13% were Hispanic (Table 1). Additionally, 41% had diabetes mellitus, 83% had hypertension, and 12% were current smokers at baseline. The average BMI was 32 kg/m\(^2\), systolic BP was 127 ± 21 mm Hg, and diastolic BP was 72 ± 12 mm Hg. The average baseline eGFR was 47 ± 17 mL/min/1.73 m\(^2\), and the median baseline UPCR was 128 (interquartile range, 53-681) mg/g. Within each 1-year exposure window, eGFR decreased by a mean of 1 ± 8 mL/min/1.73 m\(^2\) and UPCR increased by a mean of 8 ± 240 mg/g (Table S2).

Risk of Cardiac Events and Death

Over a median 11 years of follow-up (divided into successive 1-year exposure windows and 3-year follow-up windows), HF developed in 243 participants, ASCVD events developed in 238, and 374 died. Additionally, there were 681 participants who experienced kidney failure requiring replacement therapy and 155 who withdrew from the study or were lost to follow-up. Analyses simultaneously adjusted for average and slope of eGFR (otherwise unadjusted) during 1-year exposure windows, evaluating the 3-year risk of HF, ASCVD events, death, and the composite outcome, are presented in Fig 2A. Analyses adjusted for average and slope of UPCR are presented in Fig 2B.

In analyses adjusted for time-updated average and slope of eGFR and UPCR as well as baseline and time-updated covariates (Table 2), every SD lower average eGFR (19 mL/min/1.73 m\(^2\)) was associated with higher 3-year risk of HF (HR, 1.82 [95% CI, 1.39-2.44]), death (HR, 1.49 [95% CI, 1.16-1.92]), and the composite outcome (HR, 1.32 [95% CI, 1.11-1.54]), but not ASCVD events alone. Every SD greater decrease in eGFR (8 mL/min/1.73 m\(^2\) per year) was associated with higher risks of HF (HR, 1.28 [95% CI, 1.12-1.45]) and the composite outcome (HR, 1.11 [95% CI, 1.03-1.20]). Similarly, every SD higher average UPCR (136 mg/g) was associated with higher risks of HF and the composite outcome, and every SD greater increase in UPCR (240 mg/g per year) was associated with higher risks of HF, death, and the composite outcome.

Sensitivity Analyses

In fully adjusted sensitivity analyses using 2-year exposure windows instead of 1-year exposure windows (ie, using data from 3 study visits; Table S3), the relationships between average and slope of eGFR and UPCR with adverse outcomes were similar to those in the primary analyses. In analyses evaluating 1-year, instead of 3-year, outcome windows (Table S4), the results were again similar to the primary analyses except mean eGFR and slope of UPCR were no longer independently associated with death. The results were also similar to those of the primary analyses after adding adjustment for baseline total cholesterol, high-density lipoprotein, and FGF-23 (Table S5).

There was no significant interaction between average and slope of eGFR (Table S6) or between landmark period and each of the kidney function parameters (Fig S2).

Quartiles of eGFR and UPCR

We also performed analyses adjusting for quartiles of mean and slope of eGFR and UPCR in 1-year windows.
to evaluate 3-year risk of cardiovascular events (Table 3). Compared with the highest quartile of mean eGFR (≥60 mL/min/1.73 m²), the lowest quartile (eGFR ≤33 mL/min/1.73 m²) was associated with markedly higher risks of HF (HR, 5.65 [95% CI, 2.41-13.23]), death (HR, 1.95 [95% CI, 1.20-3.18]), and the composite outcome (HR, 1.84 [95% CI, 1.29-2.63]). Compared with the highest quartile of mean UPCR (≥1 mg/g), the highest quartile of UPCR (≥148 mg/g) was associated with higher risks of each of the cardiovascular end points. The highest quartile of UPCR slope (increase of ≥470 mg/g per year) was associated with higher risks of HF, death, and the composite outcome compared with the lowest quartile (decrease of ≥320 mg/g per year).

Discussion

Leveraging detailed, longitudinal data, we used a novel approach to evaluate the relationship of changing patterns of eGFR and proteinuria with cardiovascular risk. In analyses that simultaneously adjusted for average and slope of eGFR and proteinuria, we found that poorer average and worsening slope of eGFR and proteinuria over the prior 1-2 years were independently associated with increased...
3-year risk of cardiovascular disease, particularly HF. We estimated cardiac risk using clinical information obtained at varying historical time points during follow-up. To do this, we generated sliding windows in which time-updated patterns of eGFR and proteinuria could be evaluated over a long span of annual visits. This approach allowed us to use the breadth of longitudinal information available, rather than cross-sectional or static measurements, to assess the relatively short-term risk of developing adverse cardiac outcomes based on changes in kidney parameters.

The relationship of single assessments of eGFR and proteinuria with risk of HF, ASCVD events, and death has been well described in the literature. Uniquely, the present study identified that time-updated slope of eGFR and proteinuria are incrementally associated with cardiovascular risk after accounting for mean eGFR and proteinuria. A number of studies have evaluated the association of slope of eGFR with subsequent cardiac risk. These studies typically demonstrated a J-shaped association of eGFR slope with cardiac risk. For example, in 9,716 participants in the Atherosclerotic Risk in Communities (ARIC) Study in which median eGFR was 95 mL/min/1.73 m², Rebholz et al found that both substantial decrease and improvement in cystatin C–based eGFR was associated with increased risk of cardiovascular disease and mortality (HR of 1.28 [95% CI, 1.09–1.50] for ≥10% improvement in eGFR vs <10% change in eGFR). Prior studies that evaluated the association of slope of eGFR with adverse cardiac outcomes calculated the slope using 2-3 successive eGFR assessments that were performed during a baseline run-in period. Participants were then followed for many years to determine the risk of subsequent cardiac events. Thus, there was often a prolonged latent period between the final eGFR assessment and subsequent cardiac outcomes. During this latent period, there was no way to account for rapid decreases in eGFR that may have occurred in individuals whose eGFR was previously stable, or for stabilization of eGFR among individuals who previously experienced transient decreases. These differences in the methodologic approach likely account for why several prior studies found no benefit, or even increased cardiac risk, associated with an improvement in eGFR, in contrast to the present study.

More recently, our group demonstrated an association of steep decrease in baseline eGFR (using ≥± annual eGFR assessments) with increased long-term risk of death and cardiovascular events in the CRIC Study; there was no association of improvement in eGFR with risk of adverse outcomes. The present study importantly adds to our previous findings by demonstrating independent associations between the 3-year risk of major adverse cardiovascular events and even brief (ie, 1-year) time-updated intervals of eGFR and proteinuria. Data across such brief intervals are often readily available in the clinical setting and may represent new opportunities for clinicians to identify patients at high risk.

Unlike previous studies evaluating the association of slope of eGFR with cardiac outcomes, we used the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Heart Failure</th>
<th>ASCVD Events</th>
<th>Death</th>
<th>Composite Outcome</th>
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<tbody>
<tr>
<td>Mean eGFR ≤33 vs ≥60 mL/min/1.73 m²</td>
<td>5.65 (2.41–13.23)</td>
<td>1.18 (0.68–2.03)</td>
<td>1.95 (1.20–3.18)</td>
<td>1.84 (1.29–2.63)</td>
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<tr>
<td>eGFR slope ≤−5 vs ≥3 mL/min/1.73 m² per year</td>
<td>1.48 (1.09–1.99)</td>
<td>1.15 (0.87–1.52)</td>
<td>1.15 (0.89–1.48)</td>
<td>1.25 (1.04–1.49)</td>
</tr>
<tr>
<td>Mean UPCR ≥148 vs ≤51 mg/g</td>
<td>2.28 (1.29–4.04)</td>
<td>2.65 (1.53–4.60)</td>
<td>1.82 (1.11–2.99)</td>
<td>2.21 (1.56–3.12)</td>
</tr>
<tr>
<td>UPCR slope ≥470 vs ≤−320 mg/g per year</td>
<td>1.41 (1.09–1.82)</td>
<td>1.06 (0.81–1.38)</td>
<td>1.39 (1.11–1.74)</td>
<td>1.40 (1.19–1.65)</td>
</tr>
</tbody>
</table>

Values given as hazard ratio (95% CI); the results represent the lowest quartile of eGFR mean or slope compared with the reference group of highest quartile of eGFR mean or slope, respectively, and the highest quartile of UPCR mean or slope compared with the reference group of lowest quartile of UPCR mean or slope, respectively. All analyses were adjusted for baseline sex, race/ethnicity, education level, time-updated mean and slope of eGFR and UPCR, age, diabetes mellitus, hypertension, alcohol use, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, serum albumin, hemoglobin, bicarbonate, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and all parameters in the table. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-creatinine ratio.
landmark approach to assess the temporal relationship of repeated intervals of eGFR and UPCR with relatively short-term (ie, 1- and 3-year) risk of adverse cardiac events. This approach is well suited for evaluating historical, time-updated variables for which the at-risk population, as well as the relationship between risk factors and the outcome, change over time.\textsuperscript{26,40} Li et al performed similar landmark analyses using data from the African American Study of Kidney Disease and Hypertension (AASK) to evaluate the association of eGFR, eGFR slope, and UPCR with the risk of developing kidney failure.\textsuperscript{26} The authors demonstrated that the relationship between these risk factors and kidney failure varied throughout follow-up,\textsuperscript{40} highlighting the importance of using time-updated modeling approaches when evaluating the changing patterns of eGFR and UPCR over time.\textsuperscript{40} By using iterative, time-updated exposure windows, the landmark approach accounts for the changing patterns of eGFR and proteinuria within each window, as well as the changing relationship of eGFR and proteinuria with cardiac risk over time due to the changing at-risk population. Thus, this approach facilitates assessment of relatively short-term risk while leveraging the full span of exposure information available during a patient’s follow-up.

Our study has several strengths. The CRIC Study represents a diverse group of participants with mild to moderate CKD,\textsuperscript{18,19} including a large proportion of individuals with diabetes and hypertension and relatively high cardiac event rates compared with the general, non-CKD population. We pooled well-characterized, longitudinal information collected over a median of 11 years of follow-up. As a result, we had a sufficient number of data points to assess cardiac risk across a range of exposure windows and starting points. We uniquely had access to annual assessments of cystatin C–based eGFR and proteinuria (the measures of kidney function most strongly associated with cardiac risk in studies using static approaches\textsuperscript{10}) with which to assess time-updated, longitudinal relationships with cardiac risk. All cardiac events were carefully identified, with adjudication by at least 2 study physicians, minimizing the risk of misclassification of outcomes.

There are also several limitations to consider. Annual timing of eGFR and proteinuria assessments may not be generalizable to routine clinical care. Many patients with severe CKD, in particular, are monitored much more frequently than once per year, possibly capturing acute changes in eGFR. Nonetheless, the annual assessments were performed systematically across all participants, minimizing confounding by indication and informative censoring related to performance of the assessments. Additionally, many important biomarkers for cardiovascular disease risk were not included in the analyses, such as interleukin 6,\textsuperscript{41} tumor necrosis factor \(\alpha\),\textsuperscript{41} and N-terminal pro-B-type natriuretic peptide.\textsuperscript{41} These biomarkers can vary substantially over time, potentially representing meaningful changes in cardiac risk.\textsuperscript{41} Thus, to be adequately incorporated into the landmark models, these biomarkers would need to be measured annually, which was not done in the CRIC Study (and is not done in routine clinical practice).

In conclusion, we observed that short-term changes in eGFR and proteinuria provide information about cardiovascular risk in the setting of CKD that is incremental to that provided simply by level of kidney function. These findings represent possible opportunities to improve upon existing tools to identify individuals at high risk for cardiovascular events who may benefit from intensified efforts at cardiovascular risk reduction and may inform the development of dynamic risk-prediction equations that account for changes in eGFR and proteinuria over time. Should future studies confirm the value of formally incorporating longitudinal kidney function data into risk assessments, earlier and more timely preventive therapies may have an opportunity to reduce the great burden of cardiovascular disease among individuals with CKD.

## Supplementary Material

### Supplementary File (PDF)

**Figure S1:** Landmark approach to time-dated analyses of average and change in eGFR.

**Figure S2:** Change in hazard ratios across landmark periods.

**Table S1:** Linear correlations between slope and value of each parameter at different time points.

**Table S2:** Pooled characteristics of participants throughout follow-up.

**Table S3:** Three-year risk of heart failure, ASCVD events, and death by 2-year time-updated windows of mean and slope of eGFR and UPCR.

**Table S4:** One-year risk of heart failure, ASCVD events, and death by 1-year time-updated windows of mean and slope of eGFR and UPCR.

**Table S5:** Three-year risk of heart failure, ASCVD events, and death by 1-year time-updated windows of mean and slope of eGFR and UPCR: sensitivity analyses adjusted for lipid levels and FGF-23.

**Table S6:** Interaction terms for slope and average eGFR in fully adjusted models for heart failure, ASCVD, and death.

### Article Information

**CRIC Study Investigators:** Lawrence J. Appel, MD, MPH, Robert G. Nelson, MD, PhD, MS, Panduranga S. Rao, MD, Vallabhi O. Shah, PhD, MS, Raymond R. Townsend, MD, Mark L. Unruh, MD, MS.

**Authors’ Full Names and Academic Degrees:** Jordana B. Cohen, MD, MSC, Wei Yang, PhD, Liang Li, PhD, Xiaoming Zhang, MS, Zihe Zheng, MD, MHS, Paula Orlandi, MD, MSCE, Nisha Bansal, MD, MAS, Rajat Deo, MD, MTR, James P. Lash, MD, Mahboob Rahman, MD, Jang He, MD, PhD, Tarig Shafi, MBBS, MHS, Jing Chen, MD, MMS, MSc, Debbie L. Cohen, MD, Kunhiro Matussaha, MD, PhD, Michael G. Shlipak, MD, Myles Wolf, MD, Alan S. Go, MD, and Harold I. Feldman, MD, MSCE.

**Authors’ Affiliations:** Renal-Electrolyte and Hypertension Division (JBC, DLC), Department of Biostatistics, Epidemiology, and Informatics (UBC, WY, XZ, ZZ, PO, HIF), and Division of Cardiology (RD), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Department of Biostatistics,
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References


**CONCLUSION:** Short-term changes in kidney function provide information about cardiovascular risk independent of level of kidney function.

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