

## Short-Term Change in eGFR and Risk of Cardiovascular Events

Tanvir Chowdhury Turin, MD; Matthew T. James, MD; Min Jun, PhD; Marcello Tonelli, MD; Joseph Coresh, MD; Braden J. Manns, MD; Brenda R. Hemmelgarn, MD

**Background**—Lower estimated glomerular filtration rate (eGFR) on a single occasion is associated with risk of cardiovascular events; whether the degree of change in eGFR during a 1-year period adds prognostic information is unknown.

**Methods and Results**—We included adults who had  $\geq 2$  outpatient eGFR measurements ( $\geq 6$  months apart) during a 1-year accrual period in Alberta, Canada. According to recent guidelines, we used a change in eGFR category ( $\geq 90$ , 60 to 89, 45 to 59, 30 to 44, 15 to 29, and  $< 15$  mL/min per  $1.73$  m<sup>2</sup>), and the presence/absence of a  $\geq 25\%$  change from baseline to classify participants into 5 groups: certain drop, uncertain drop, stable (no change), uncertain rise, and certain rise. We calculated adjusted rates of cardiovascular events (per 10 000 person-years) for each group. We estimated the adjusted risks of cardiovascular events associated with each category of change in eGFR, in reference to stable kidney function. Among the 526 388 participants, 76.1% ( $n=400$  560) had stable, 2.6% ( $n=13$  668) had a certain drop, and 3.3% ( $n=17$  499) had a certain rise in eGFR. Compared with participants with stable kidney function, adjusted risks of myocardial infarction, heart failure, and stroke were 27%, 51%, and 20% higher, respectively, for those with a certain drop in kidney function. After adjusting for the last eGFR at the end of the accrual period, the observed association diminished.

**Conclusion**—Clinically relevant changes in eGFR are associated with increased risk of cardiovascular events. However, most of the apparent increase in risk can be accounted for by assessing comorbidity and baseline kidney function. (*J Am Heart Assoc.* 2014;3:e000997 doi: 10.1161/JAHA.114.000997)

**Key Words:** Canada • cardiovascular diseases • clinical epidemiology • kidney function • short-term change

Chronic kidney disease (CKD) is a major public health concern,<sup>1</sup> prevalent in 10% to 16% of the adult population. It is associated with an increased risk of adverse outcomes, including cardiovascular (CV) events, in both general and high-risk populations.<sup>2–8</sup> While studies consistently show a graded association between severe CKD and adverse clinical outcomes,<sup>6–8</sup> these reports focused on assessment of kidney function at 1 point in time and were not designed to examine the relationship between changes in kidney function on future risk. Considering the magnitude of

changes in estimated glomerular filtration rate (eGFR) in addition to baseline eGFR alone might yield additional prognostic information.

The associations between change in kidney function over time and adverse outcomes have been reported in a few population-based studies.<sup>9–15</sup> These studies predominantly defined rate of change in kidney function based on repeated measures of eGFR over periods ranging from 3 to 10 years, which are not helpful in many clinical settings. While an annual assessment of change in eGFR is arguably the most practical means for clinical evaluation of CKD progression, the association between changes in kidney function during 1 year and risk of CV events remains unknown. Thus, using a population-based cohort from a single province in Canada, we evaluated the associations of short-term change in kidney function with the risk of specific CV events: hospitalization for acute myocardial infarction (AMI), congestive heart failure (CHF), and stroke.

From the Departments of Family Medicine (T.C.T.), Community Health Sciences (T.C.T., M.T.J., B.J.M., B.R.H.), and Medicine (M.T.J., M.J., B.J.M., B.R.H.), Libin Cardiovascular Institute (T.C.T., M.T.J., B.J.M., B.R.H.) and Institute of Public Health (T.C.T., M.T.J., B.J.M., B.R.H.), University of Calgary, Calgary, Alberta, Canada; Department of Medicine, University of Alberta, Edmonton, Alberta, Canada (M.T.); Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (J.C.).

**Correspondence to:** Tanvir Chowdhury Turin, MD, PhD, Department of Family Medicine, Room G012F, Health Sciences Center, 3330 Hospital Dr NW, Calgary, Alberta, Canada T2N 4N1. E-mail: turin.chowdhury@ucalgary.ca  
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### Methods

#### Design, Setting, Population, and Data Sources

We conducted a population-based cohort study of all adults  $\geq 18$  years of age in Alberta, Canada, who had  $\geq 2$  outpatient

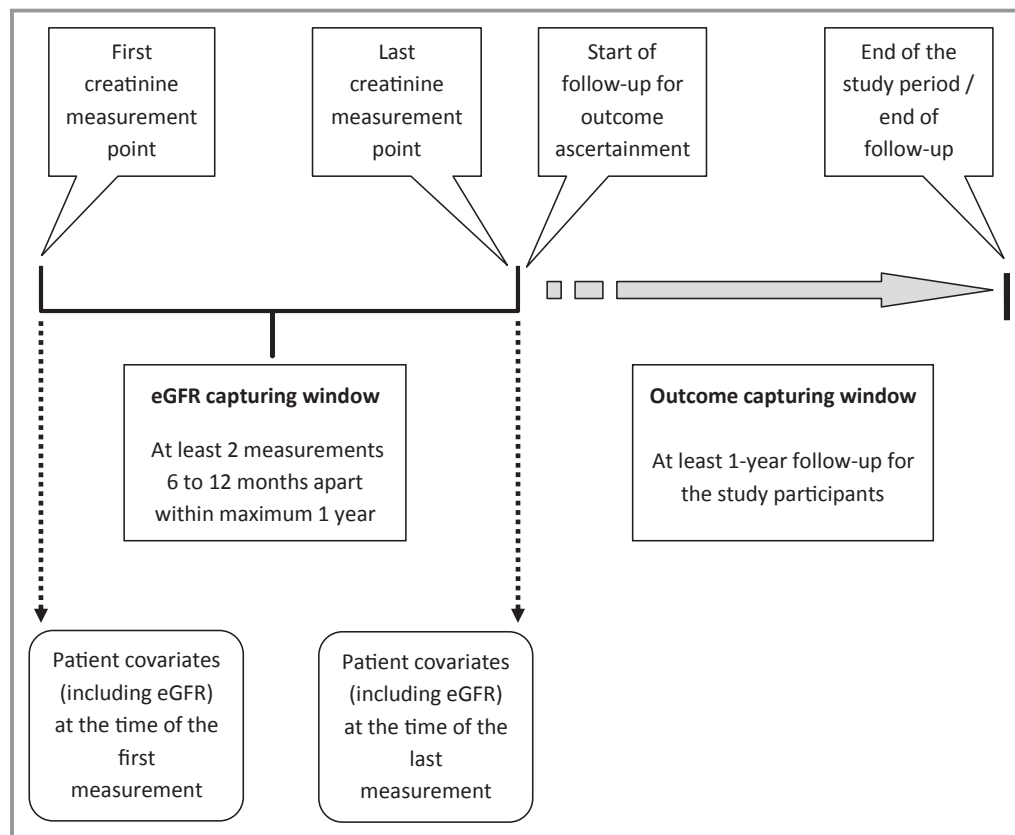
creatinine measurements ( $\geq 6$  months apart) within a 1-year period (Figure 1), using the data repository of the Alberta Kidney Disease Network (AKDN).<sup>16–18</sup> The eGFR capture time frame was from May 2002 to March 2008, with follow-up to March 2009 (ensuring  $\geq 1$  year of follow-up for ascertainment of outcomes for all participants). Among the 1 818 381 patients with  $\geq 1$  outpatient serum creatinine measurement, there were 865 819 participants for whom  $\geq 2$  measurements were available in a 1-year period. We further excluded individuals with: a history of CV events before cohort entry including AMI, CHF, or stroke;  $>24$  measurements in a 1-year period (possibly indicating unstable kidney function or frequent illness); baseline eGFR  $<15$  mL/min per  $1.73$  m<sup>2</sup>; or measurements separated by  $\leq 6$  months (Figure 2).

### Change in Kidney Function

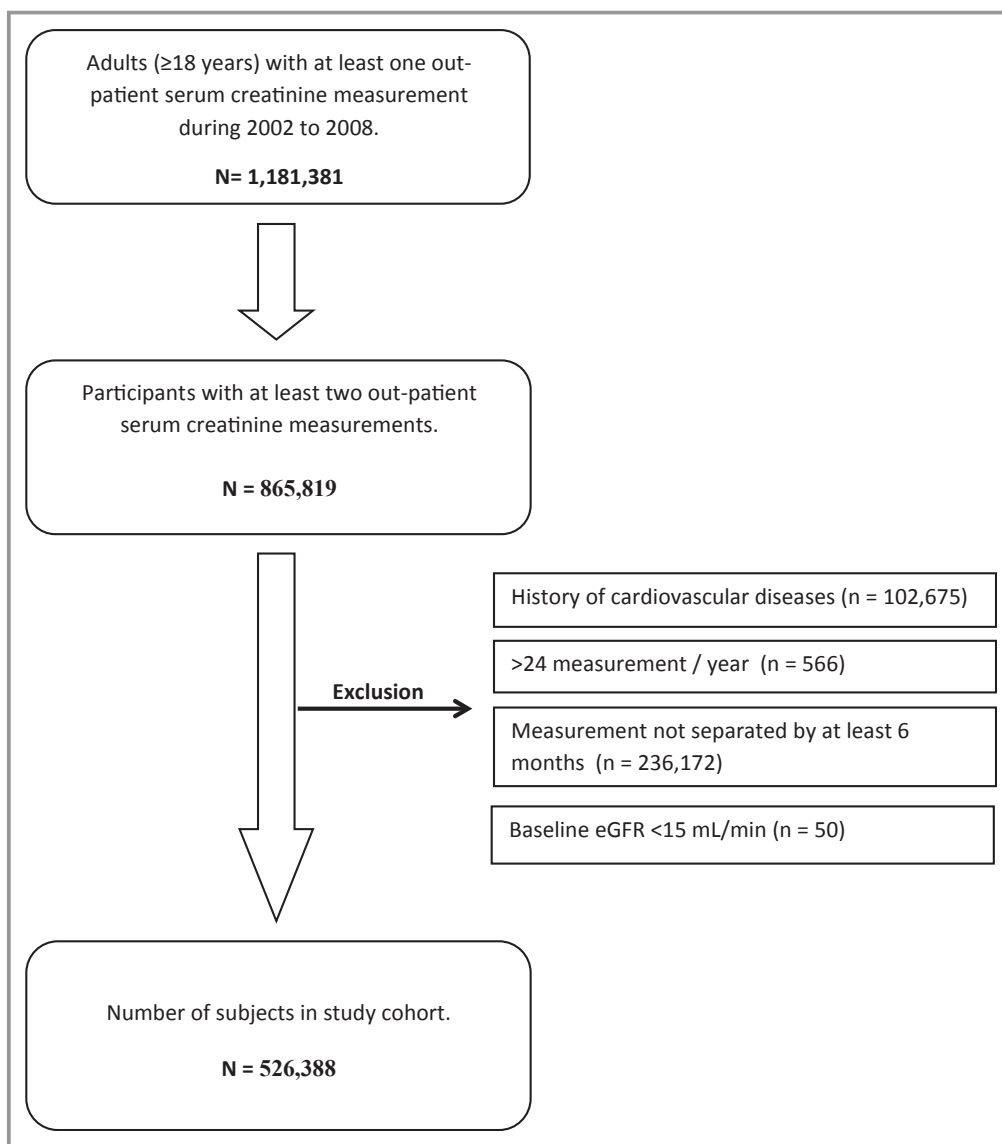
The first and last outpatient creatinine measurements during the 1-year accrual period were used to estimate GFR at the start and end of the accrual period by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation<sup>19</sup> as recommended in the recent Kidney Disease

Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney.<sup>20</sup> Although data on race were not available from the data sources,  $<1\%$  of the Alberta population is black.<sup>21</sup> eGFR was divided into the following categories:  $\geq 90$ , 60 to 89, 45 to 59, 30 to 44, 15 to 29, and  $<15$  mL/min per  $1.73$  m<sup>2</sup>, respectively.

Change in kidney function (based on the first and last eGFR measurements) was defined according to recent guidelines<sup>20</sup> by change in eGFR category with confirmation of a significant change based on the magnitude of the percent change in eGFR ( $[(\text{last eGFR} - \text{first eGFR}) / \text{first eGFR}] \times 100$ ). The groups for change in kidney function were thus defined as “certain drop” (drop in eGFR category with  $\geq 25\%$  decrease in eGFR), “uncertain drop” (drop in eGFR category with  $<25\%$  decrease in eGFR), “stable” (no change in eGFR category), “uncertain rise” (rise in eGFR category with  $<25\%$  rise in eGFR), and “certain rise” (rise in eGFR category with  $\geq 25\%$  increase in eGFR). Similar to other published studies,<sup>14,22–24</sup> a 25% change in eGFR was used to define certainty of change, because changes of this magnitude are unlikely to represent intra-assay<sup>25</sup> or intraindividual variation in serum creatinine across measurements.<sup>11,26,27</sup>



**Figure 1.** Overview of cohort creation and study period. eGFR indicates estimated glomerular filtration rate.



**Figure 2.** Study cohort formation. eGFR indicates estimated glomerular filtration rate.

## Covariates

Participants' sociodemographic characteristics were determined from the administrative data sources of the provincial health ministry (Alberta Health). Socioeconomic status was categorized as high income (annual adjusted taxable family income  $\geq$ \$39 250 Canadian Dollar), low income (annual adjusted taxable family income  $<$ \$39 250 Canadian Dollar), low income with subsidy (receiving social assistance), and pensioners (aged  $\geq$ 65 years) based on Government of Alberta health care insurance records.<sup>28</sup> Presence of diabetes mellitus and hypertension was identified from hospital discharge records and physician claims based on validated algorithms.<sup>29,30</sup> Other comorbid conditions based on the Deyo classification of Charlson comorbidities were identified from the physician claims and hospitalization records by using

validated *International Classification of Diseases, 9th Edition, Clinical Modifications* and *International Classification of Diseases, 10th Edition, Clinical Modification* coding algorithms.<sup>31</sup> Albuminuria was estimated by urine albumin:creatinine ratio or urine dipstick based on outpatient random spot urine measurements. Albuminuria was categorized as normal, mild, heavy, or unmeasured based on albumin:creatinine ratio (normal [ratio  $<$ 30 mg/g], mild [ratio 30–300 mg/g], or heavy [ratio  $>$ 300 mg/g]) or urine dipstick ([urine dipstick negative] of mild [urine dipstick trace or 1+] or heavy [urine dipstick 2+]), as previously described.<sup>8,32</sup>

## Outcome Ascertainment

Participants were followed from the date of the last creatinine measurement until study end (March 31, 2009). The outcomes

were hospitalization for AMI, CHF, and stroke, identified from the Alberta Health hospitalization databases<sup>16</sup> based on validated algorithms.<sup>33–35</sup>

## Statistical Analyses

The differences in continuous and categorical variables across the 5 groups for change in kidney function were assessed by using ANOVA and  $\chi^2$  tests, as appropriate. Adjusted rates (per 10 000 person-years) for each group of change in kidney function were calculated by using Poisson regression, adjusting for covariates as in Table 1. We considered 2 perspectives

regarding adjustment for the covariates (including eGFR)—adjustment for the covariates extracted at the time point of the first eGFR measurement and adjustment for the covariates extracted at the time point of the last eGFR measurement (Figure 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 CV outcomes associated with each group of change in kidney function, with stable kidney function (no category change) serving as the reference. Hazard ratios were also estimated separately for the first and the last measurement perspectives. The proportional hazards assumption was

**Table 1.** Baseline Characteristics of Study Participants by 1-Year Change in Kidney Function Stage

	1-Year Change in Kidney Function, n (%)					P Value
	Certain Drop, 13 668 (2.6)	Uncertain Drop, 55 184 (10.5)	Stable, 400 560 (76.1)	Uncertain Rise, 39 477 (7.5)	Certain Rise, 17 499 (3.3)	
Age, mean (SD), y	58.9 (17.2)	56.7 (14.5)	53.0 (16.5)	56.2 (14.2)	56.4 (17.1)	<0.001
Female gender	65.3	59.2	59.9	57.4	65.6	<0.001
Aboriginal	3.1	1.8	2.5	1.7	2.7	<0.001
Diabetes	18.8	13.3	11.8	12.5	13.6	<0.001
Hypertension	48.3	38.9	32.9	37.3	41.2	<0.001
Albuminuria						
Normal	46.7	56.7	58.7	57.8	51.0	<0.001
Mild	8.7	5.9	5.6	5.9	8.1	
Heavy	4.6	1.4	1.0	0.9	1.9	
Unmeasured	39.9	36.0	34.7	35.3	39.1	
eGFR at baseline, mL/min per 1.73 m <sup>2</sup>						
≥90	45.8	72.1	48.0	0	0	<0.001
60 to 89	38.7	21.1	44.9	75.5	52.3	
45 to 59	10.1	5.6	5.0	19.3	30.1	
30 to 44	4.3	1.1	1.7	4.6	13.2	
15 to 29	1.2	0.1	0.5	0.7	4.0	
COPD	18.5	15.7	15.0	15.2	17.6	<0.001
Cancer	9.7	6.3	5.5	5.7	7.6	<0.001
Peptic ulcer disease	3.2	2.4	2.4	2.4	3.1	<0.001
Rheumatic disease	3.3	2.2	1.9	2.0	2.6	<0.001
Socioeconomic status						
Pensioner	41.1	31.4	27.2	28.7	33.8	<0.001
Low	12.3	13.2	12.5	13.5	11.6	
With subsidy	5.2	3.3	3.7	3.1	4.8	
eGFR, mean (SD), mL/min per 1.73 m <sup>2</sup>						
First measurement	84.5 (23.0)	86.9 (17.4)	89.5 (20.5)	77.9 (14.6)	62.8 (16.9)	<0.001
Last measurement	55.9 (17.9)	76.1 (15.8)	89.5 (20.6)	87.9 (16.1)	87.9 (21.0)	<0.001

Data are in %, unless mean (SD). Totals do not always add to 100% because of rounding. The differences in continuous and categorical variables across the 5 groups for change in kidney function were assessed using ANOVA and  $\chi^2$  tests, as appropriate. COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

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 or left the province.

We performed several sensitivity analyses to confirm the robustness of our study findings. We performed separate analysis among men and women, and we repeated analyses for participants who had only 2 measurements during the 1-year period and for the participants with >2 measurements. We also analyzed participants stratified into age <65 and ≥65 years. All of these analyses were performed by using separate models adjusting for the covariates measured at either the first and last eGFR measurement. Statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc), and STATA version 12.0 (StataCorp).

## Results

Participant characteristics by change in kidney function groups are shown in Table 1. Of the 526 388 eligible

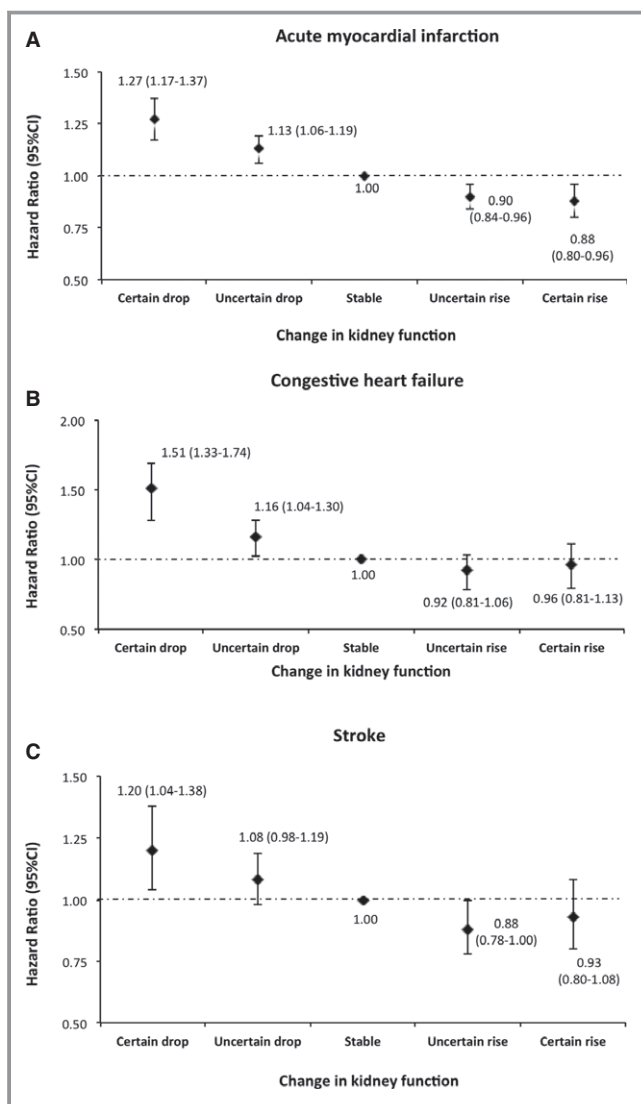
participants, 76.1% (n=400 560) had stable (no change in eGFR category), 2.6% (n=13 668) had a certain drop, and 3.3% (n=17 499) had a certain rise in kidney function. Participants who experienced a drop or rise in kidney function were older, more likely to be female, and had a higher prevalence of comorbidities, compared with those with stable kidney function.

There were 5268 (1.0%) hospitalizations for AMI, 3130 (0.6%) for CHF, and 4174 (0.8%) for stroke over a median follow-up of 3.5 years. The adjusted rates of AMI, CHF, and stroke are shown in Table 2. After adjustment for the first (baseline) eGFR measurement, the highest adjusted rates were observed in individuals with a certain drop: AMI (rate 19.7 per 10 000 person-years; 95% CI 17.1 to 22.3), CHF (rate 7.1 per 10 000 person-years; 95% CI 6.0 to 8.2), and stroke (rate 12.8 per 10 000 person-years; 95% CI 10.9 to 14.6). However, after multivariable adjustment at the last eGFR measurement in the 1-year accrual period, the highest adjusted rates were observed in individuals with a certain rise for CHF (rate 5.1 per 10 000 person-years; 95% CI 4.3 to 6.0) and stroke (rate 11.4 per 10 000 person-years; 95% CI 9.7

**Table 2.** Acute Myocardial Infarction, Congestive Heart Failure, and Stroke Rates, per 10 000 Person-Years, by 1-Year Change in Kidney Function

	1-Year Change in Kidney Function				
	Certain Drop	Uncertain Drop	Stable	Uncertain Rise	Certain Rise
Patients, n	13 668	55 184	400 560	39 477	17 499
<i>Acute myocardial infarction</i>					
Events, n (%)	236 (1.72)	652 (1.18)	3774 (0.94)	407 (1.03)	199 (1.14)
Adjusted for covariates at first measurement					
Rate (95% CI)	19.7 (17.1 to 22.3)	18.5 (17.0 to 20.1)	16.0 (15.3 to 16.7)	14.2 (12.7 to 15.7)	12.9 (11.0 to 14.9)
Adjusted for covariates at last measurement					
Rate (95% CI)	15.1 (13.0 to 17.2)	15.1 (13.8 to 16.4)	16.0 (15.3 to 16.7)	17.3 (15.5 to 19.1)	16.2 (13.9 to 18.5)
<i>Congestive heart failure</i>					
Events, n (%)	234 (1.71)	408 (0.74)	2083 (0.52)	238 (0.60)	167 (0.95)
Adjusted for covariates at first measurement					
Rate (95% CI)	7.1 (6.0 to 8.2)	5.2 (4.6 to 5.9)	4.2 (3.8 to 4.5)	4.1 (3.2 to 4.4)	3.8 (3.4 to 4.8)
Adjusted for covariates at last measurement					
Rate (95% CI)	5.0 (4.2 to 5.8)	4.0 (3.5 to 4.5)	4.1 (3.7 to 4.4)	4.7 (3.9 to 5.3)	5.1 (4.3 to 6.0)
<i>Stroke</i>					
Events, n (%)	213 (1.56)	509 (0.92)	2943 (0.73)	313 (0.79)	196 (1.12)
Adjusted for covariates at first measurement					
Rate (95% CI)	12.8 (10.9 to 14.6)	11.2 (10.1 to 12.3)	10.0 (9.5 to 10.6)	8.9 (7.9 to 10.0)	9.6 (8.1 to 11.2)
Adjusted for covariates at last measurement					
Rate (95% CI)	10.3 (8.7 to 11.9)	9.5 (8.6 to 10.5)	10.1 (9.5 to 10.6)	10.5 (9.2 to 11.7)	11.4 (9.7 to 13.1)

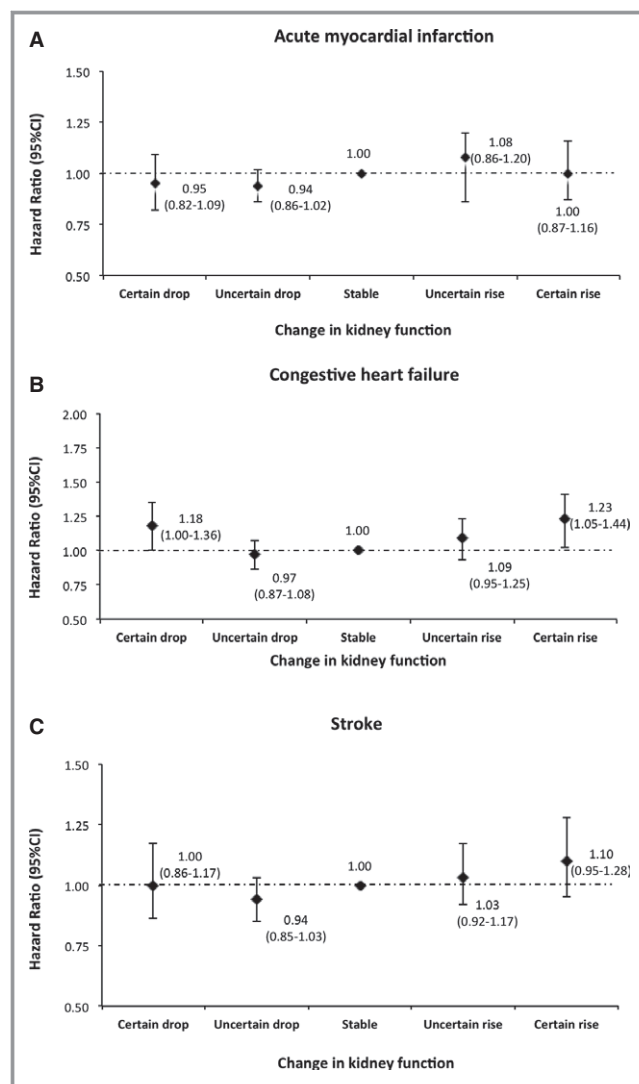
Rates are adjusted for age, sex, diabetes, hypertension, socioeconomic status, eGFR, albuminuria, and history of cancer, chronic obstructive pulmonary disease, peptic ulcer disease, and rheumatic disease at the corresponding time points. eGFR indicates estimated glomerular filtration rate.



**Figure 3.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement. Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.

to 13.1) and for uncertain rise for AMI (rate 17.3 per 10 000 person-years; 95% CI 15.5 to 19.1).

Compared with participants with stable kidney function, hazard ratios, adjusted for covariates including eGFR at the first measurement, for AMI, CHF, and stroke were 27%, 51%, and 20% higher, respectively, for those with a certain drop in kidney function. Adjusted hazard ratios were also increased, but to a lesser extent, in participants with an uncertain drop in kidney function (Figure 3). In contrast, hazard ratios associated with a significant drop in eGFR were attenuated after adjustments by using covariates at the last eGFR measurement (Figure 4) and were no longer increased for the outcomes of myocardial infarction or

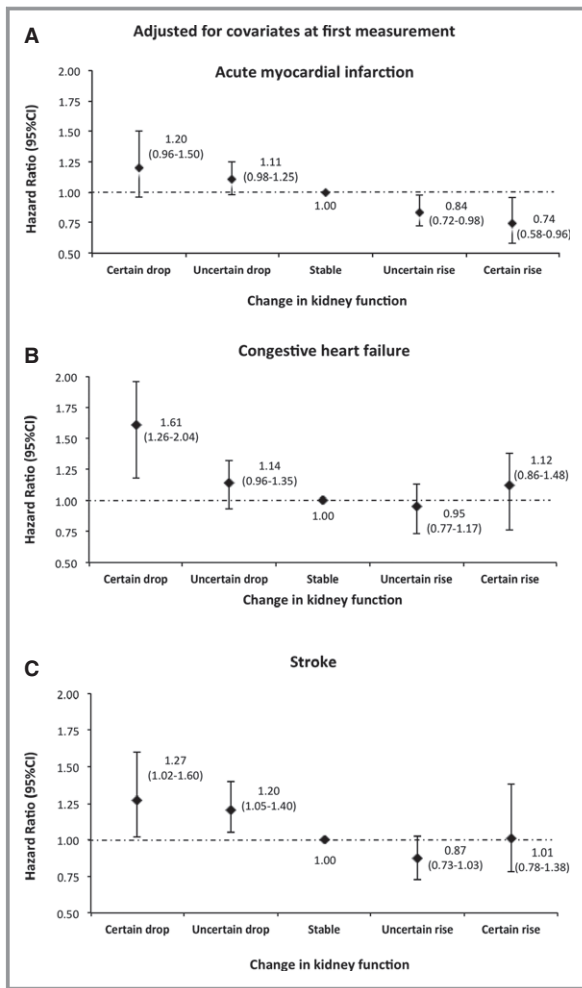


**Figure 4.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement. Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

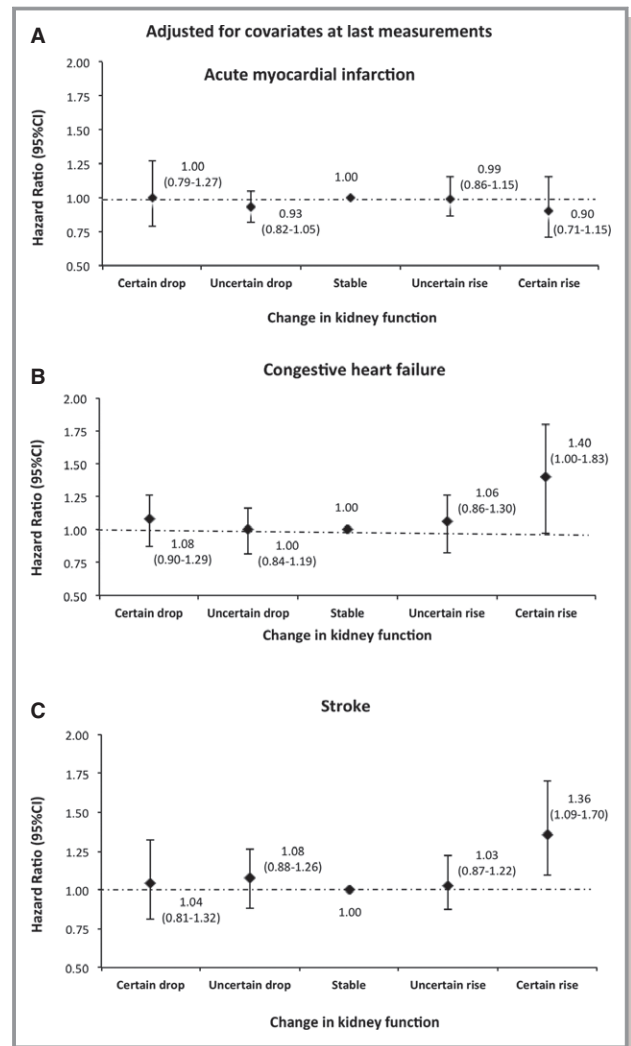
stroke. However, a U-shaped relationship was observed for the outcome of hospitalization for CHF, with both certain drop and rise being associated with statistically significant but clinically small increases (18% and 23% higher risk, respectively) in comparison to stable kidney function.

We further assessed the risk of hospitalization for AMI, CHF, and stroke associated with the last eGFR measurement specifically, including adjustment for covariates at the time of the last eGFR in the 1-year accrual period. Relative to eGFR  $\geq 90$ , the adjusted risks of AMI associated with eGFR categories of 60 to 89, 45 to 59, 30 to 44, and 15 to 29 were 1.26 (95% CI 1.16 to 1.38), 1.56 (95% CI 1.39 to 1.75),





**Figure 5.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement among participants with 2 measurements (median and below). Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.



**Figure 6.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement among participants with 2 measurements (median and below). Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

1.83 (95% CI 1.59 to 2.10), and 2.38 (95% CI 1.97 to 2.87), respectively, demonstrating the increased risk of AMI with lower categories of kidney function based on the last eGFR measure. Similar increases in risk with lower levels of the last eGFR measurement were observed for the outcomes of CHF and stroke.

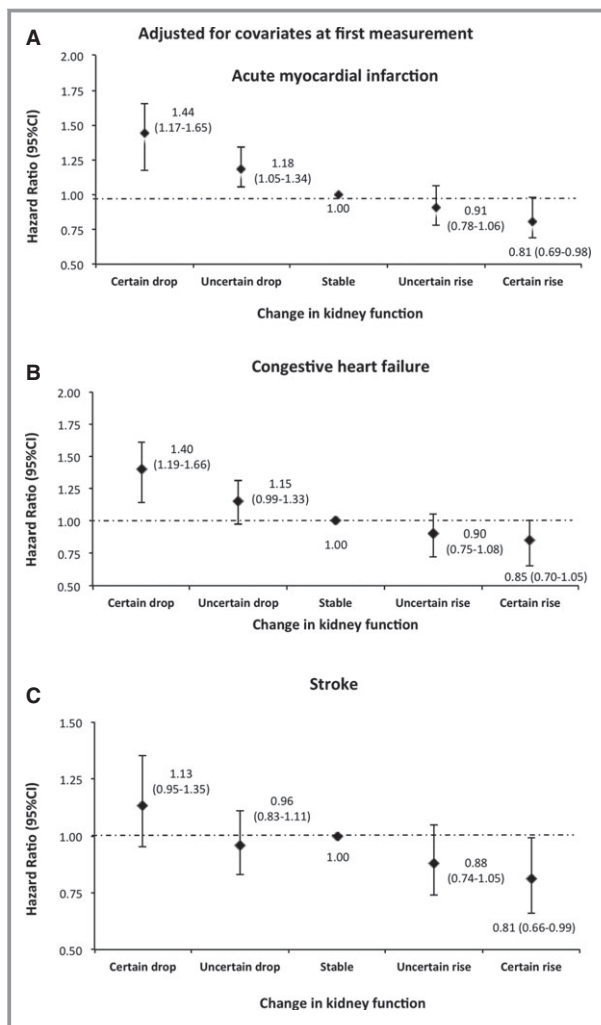
**Sensitivity Analysis**

In analyses stratified according to the number of available serum creatinine measurements for each participant, similar results were observed for participants with greater than the median (>2) and for those with the median or fewer (≤2) number of measurements during the accrual period

(Figures 5 through 8). Similar results were observed when men and women were analyzed separately (Figures 9 through 12). We also found a similar association between change in kidney function and the risk of each of the CV outcomes in analyses stratified by age <65 and ≥65 years (Figures 13 through 16).

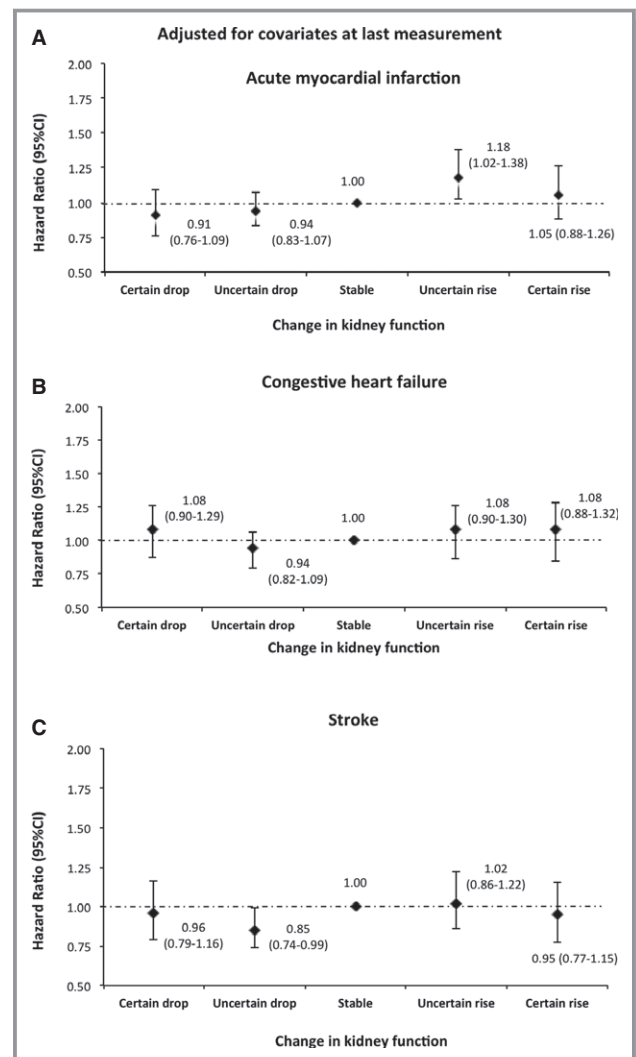
**Discussion**

In this large community-based cohort, we explored the association between change in eGFR over a 1-year period and risk of CV events, using definitions for change in kidney function based on recent international guidelines. We found



**Figure 7.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement among participants with  $\geq 3$  measurements (above median). Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.

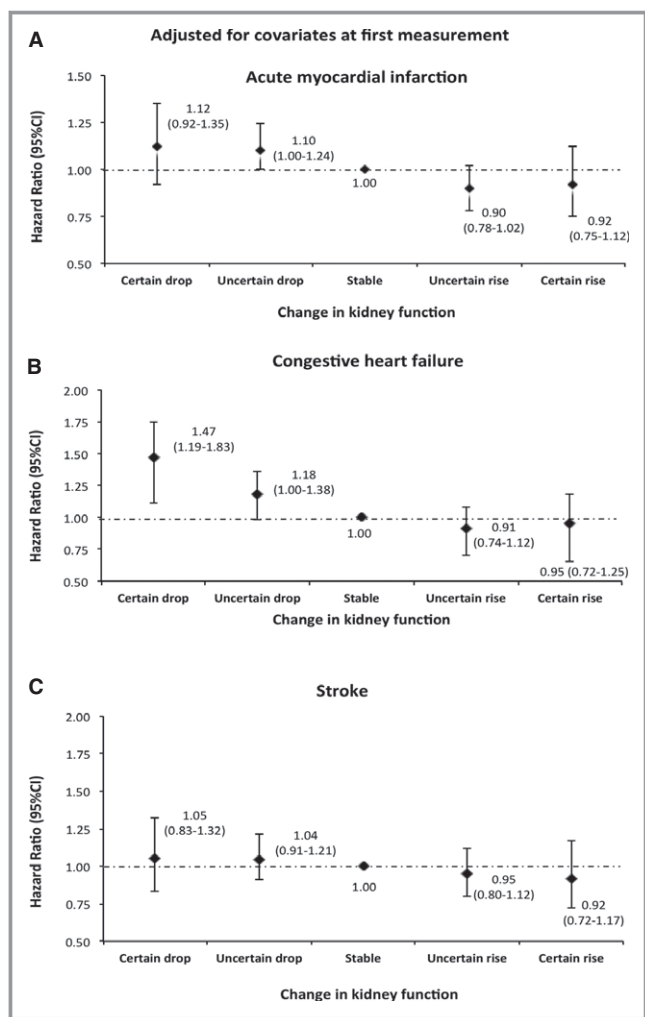
that a certain drop in eGFR (change in eGFR category accompanied by a 25% decline from the baseline eGFR) was associated with an increased risk of AMI, CHF, and stroke—a risk that was independent of baseline kidney function, albuminuria, and other covariates. However, when the risk of CV events was assessed taking into account the last eGFR measurement, 1-year changes in kidney function were no longer associated with increased risk of AMI or stroke and were only associated with a small increase in the risk of CHF. This suggests that incorporation of retrospective changes in kidney function during the preceding year does not add important prognostic information about the risk of CV events, compared with simply considering the last available measurement of eGFR and clinical features available at that time.



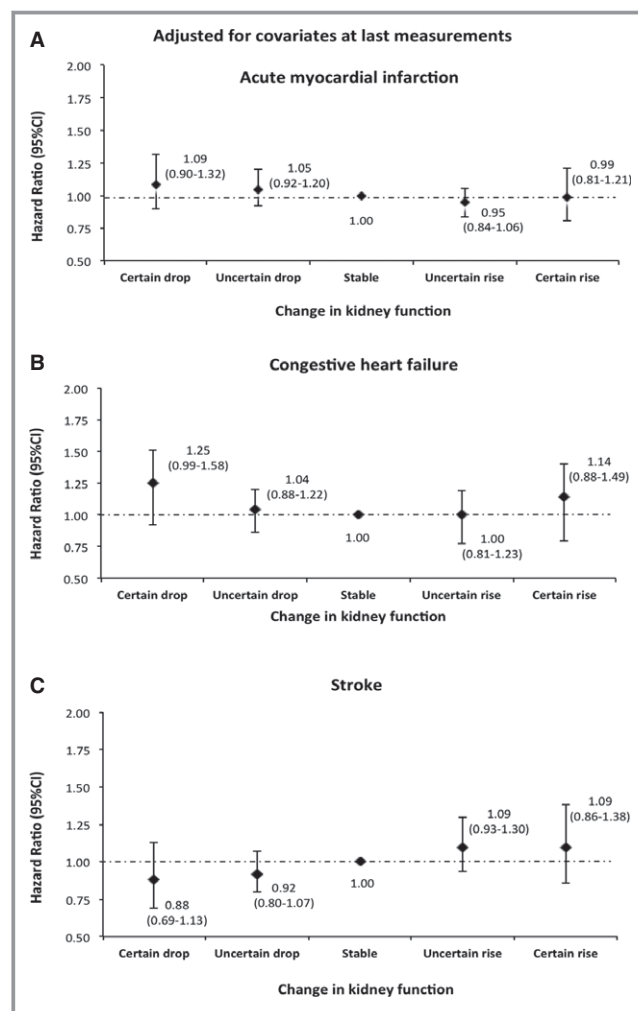
**Figure 8.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement among participants with  $\geq 3$  measurements (above median). Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

Our results regarding change in kidney function and risk of CV events are consistent with other reports. In a study of 4308 community dwelling older adults, rapid decline in kidney function (defined as  $>3$  mL/min per  $1.73$  m<sup>2</sup> per year) was associated with a 70% increased risk of CVD death.<sup>11</sup> Cheng et al also reported that a decline in eGFR  $>20\%$  during 18 months was associated with a  $>2$ -fold increased risk of death from coronary heart disease (CHD) or stroke.<sup>14</sup> Matsushita et al,<sup>9</sup> analyzing the Atherosclerosis Risk In Communities ARIC study cohort, reported that patients with the greatest annual decline in eGFR (change of  $-52.67\%$  to  $-5.65\%$ ) were at significantly greater risk for CHD events compared with patients with minimal annual decline (change





**Figure 9.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement among men. Models were adjusted for age, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.

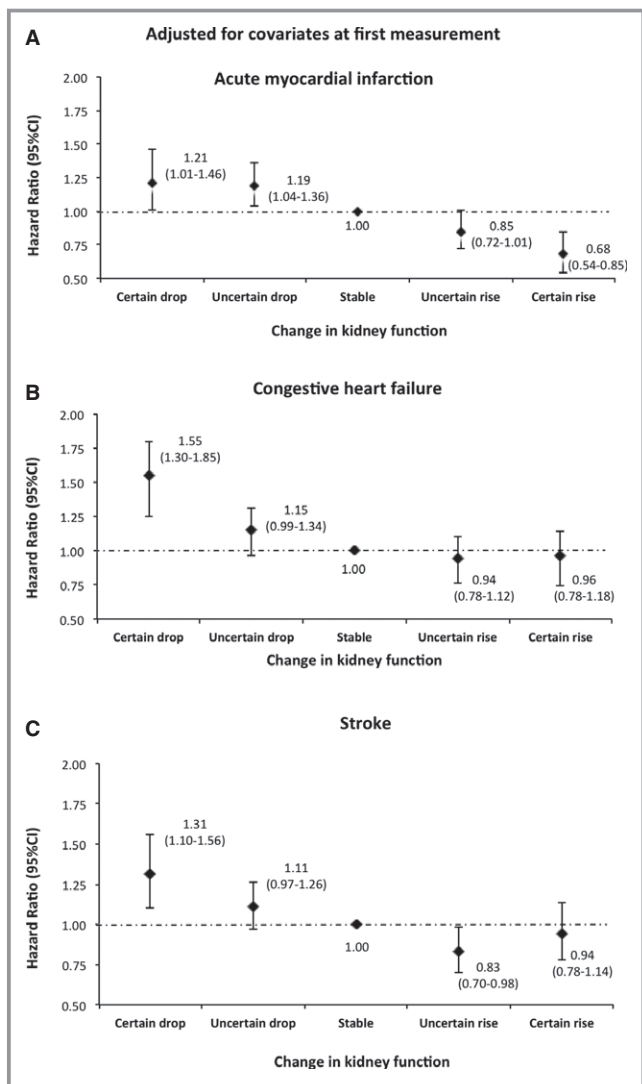


**Figure 10.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement among men. Models were adjusted for age, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

of  $-0.47\%$  to  $-0.33\%$ ). Using the Cardiovascular Health Study, Shlipak et al compared the associations of changes in kidney function during the first 7 years with the incidence of CVD and reported that rapid decline (defined as  $>3$  mL/min per  $1.73$  m<sup>2</sup> per year) was associated with 42% increased risk of myocardial infarction, 24% increased risk of heart failure, and 11% increased risk of stroke.<sup>15</sup> These studies, however, did not consider the adjustment at last measurements but rather considered the issue of adjustment at the first measurement only.<sup>11,14,15</sup>

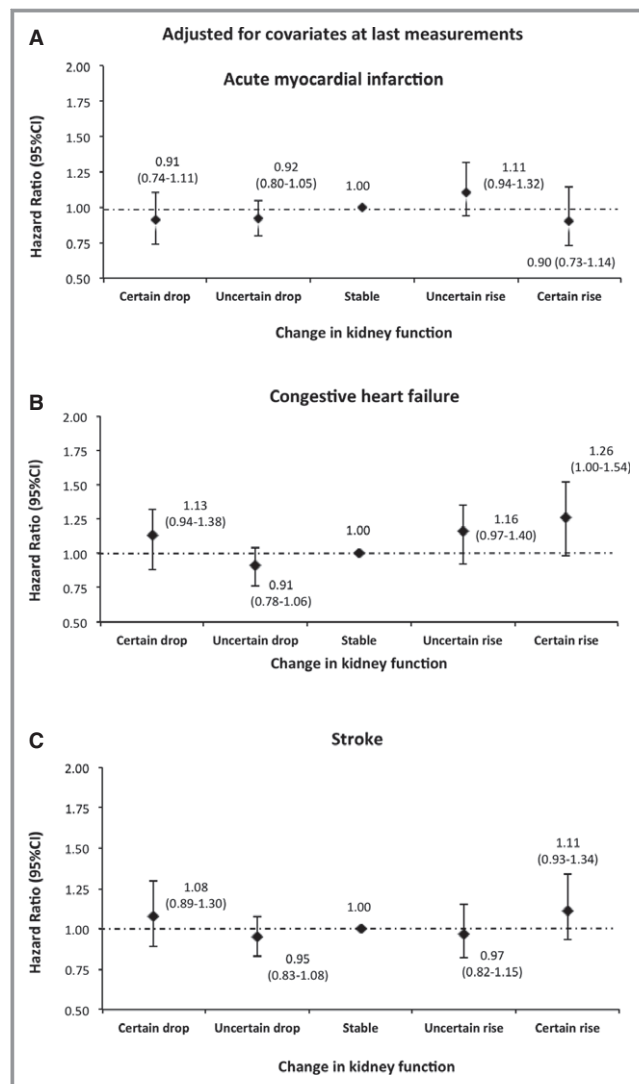
We found that the association between 1-year decline in kidney function and risk of atherosclerotic CV events (AMI and stroke) was no longer present after adjustment for kidney function and covariates at the last measurement in the 1-year accrual period. Further, the lower levels of kidney function

itself at the last measurement showed a graded increase in risk of AMI and stroke, independent of the previous change. Similar to our results, Matsushita et al<sup>9</sup> reported that, regarding the association between a decrease in eGFR with CHD events (defined as a definite or probable myocardial infarction, definite CHD death, or coronary revascularization procedure), past changes of eGFR (during 9 years) were less useful in estimating risk of incident CHD. The authors reported that the higher risk for incident CHD observed in those with the most rapid decline became nonsignificant after adjustment for eGFR and covariate levels at the last measurement. Similar relationships have been reported between short-term changes in kidney function and progression to end-stage kidney disease.<sup>22</sup> Conversely, we found that both a certain rise and a certain drop in eGFR were associated



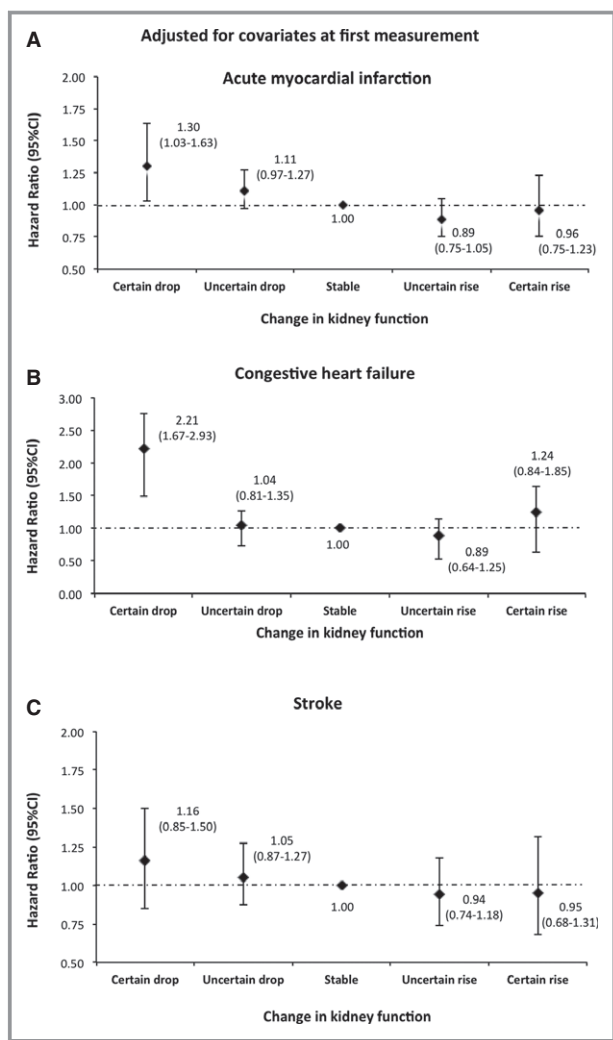
**Figure 11.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement among women. Models were adjusted for age, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.

with higher risks of hospitalization for CHF. Interestingly, this observed phenomenon was also present for the outcome of all-cause mortality, which we have reported previously.<sup>24</sup> We observed that, even after adjustment for covariates at the point of last eGFR measurement, the certain rise and certain drop in kidney function within 1-year was associated with 41% and 46% increased risk of all-cause death, respectively. A similar relationship between change in eGFR and mortality was reported in other studies.<sup>10,12</sup> The explanation for the association between certain rise in eGFR and increased risk of CHF is not apparent, but this finding might be due to lower serum creatinine generation as a result of reduced muscle mass associated with chronic illness and frailty.<sup>13,36</sup>

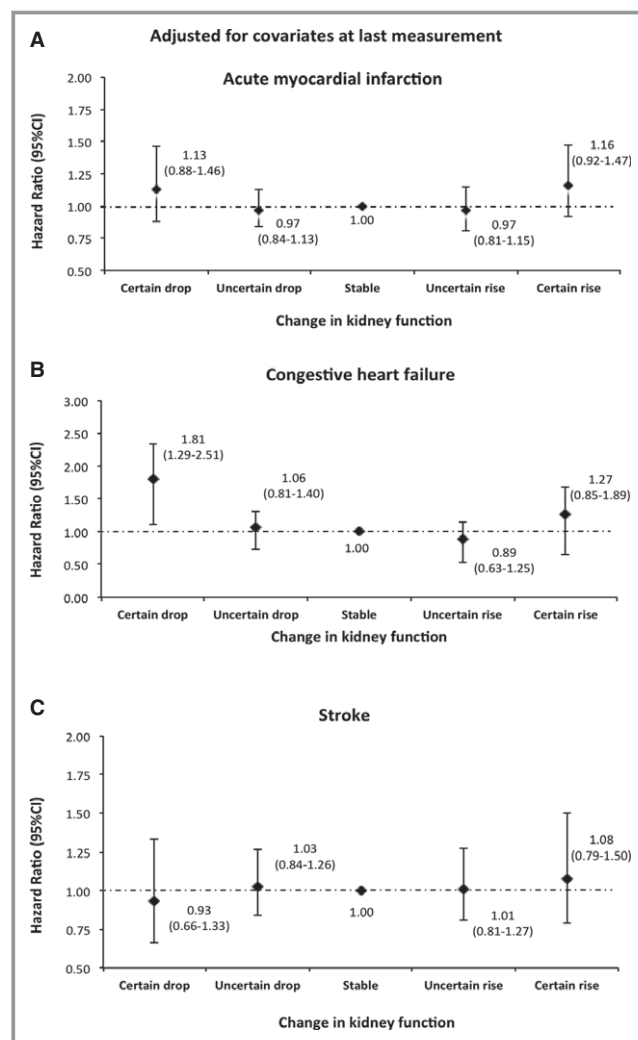


**Figure 12.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement among women. Models were adjusted for age, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

Our results suggest that a simple cross-sectional assessment at the last visit may be adequate in assessing the association between kidney function and subsequent risk of CV events. This may be attributed to the point that prognostication from retrospective assessment of change in eGFR on atherosclerotic risk, in contrast to the prospective assessment, is already captured in the patient's achieved level of kidney function. We also could not conduct rigorous analysis of the predictors of variation in eGFR in our cohort. Though the results of such an analysis would be unlikely to affect the conclusions of the current study, our findings demonstrate how models for the prediction of subsequent



**Figure 13.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement among participants <65 years. Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.

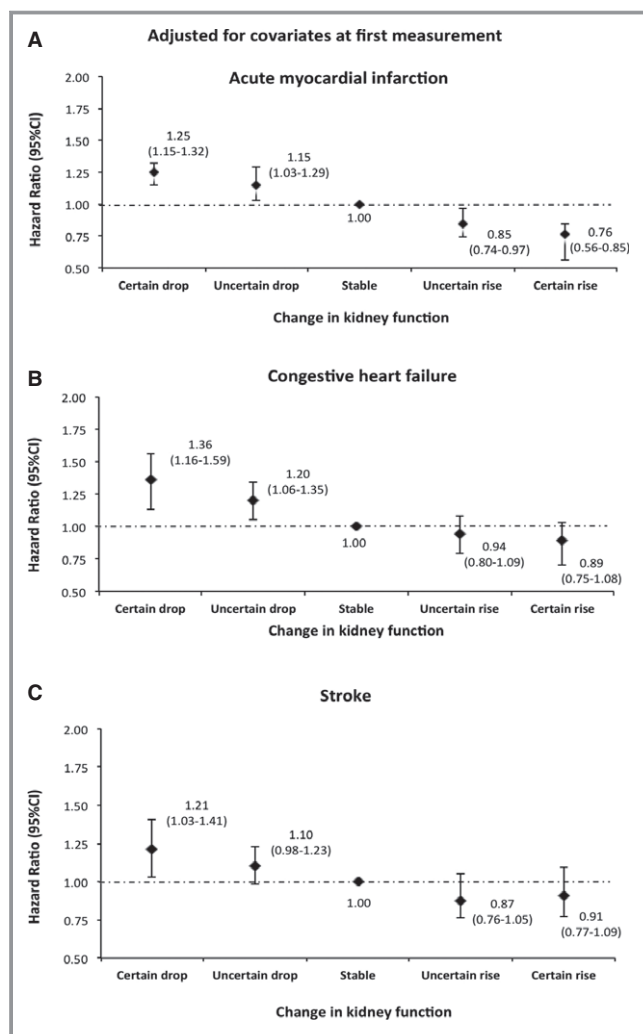


**Figure 14.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement among participants aged <65 years. Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

decline in eGFR could also be applied to estimate predicted risks of subsequent atherosclerotic events.

There are a number of strengths in our study, including the use of a large community-dwelling population with a wide range of eGFR. We were also able to assess the effect of 1-year change in eGFR adjusted for both baseline and last estimates of kidney function to assess the independent effect of change in kidney function after accounting for the risk conferred by absolute levels of eGFR measured at specific points in time. There are few limitations of our study that need to be mentioned. First, our study cohort was limited to patients who had outpatient serum creatinine measured as part of routine care and therefore does not include patients who did not access medical services.

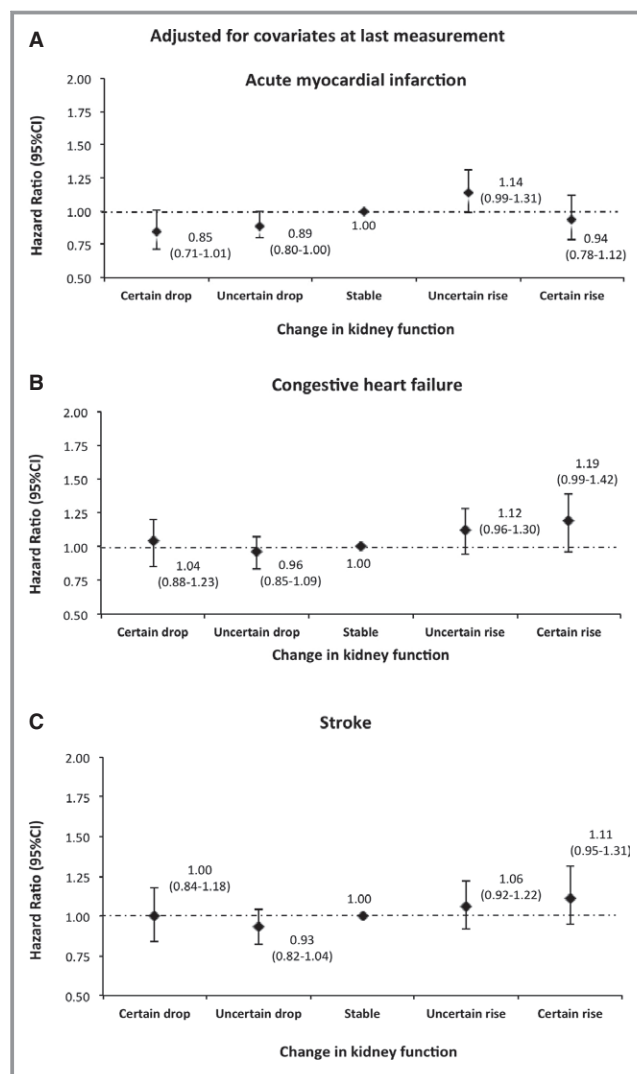
Further, information on the indication for serum creatinine measurement was not available. Therefore, our cohort may have resulted in preferential selection of people with comorbidity, although we were able to adjust for measured comorbidity in our analyses. Nonetheless, because, for risk prediction in clinical practice, we were interested in outcomes among people with available estimates of eGFR, this limitation does not nullify our results. Finally, although we adjusted for possible confounding factors (eg, demographic factors, measured comorbidities, kidney function, and albuminuria), we were not able to adjust for variables that may be associated with change in kidney function (eg, body mass index, blood pressure control, cause of kidney



**Figure 15.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the first measurement among participants aged  $\geq 65$  years. Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the first measurement.

disease, and smoking status)—thus, we cannot exclude the possibility of residual confounding among estimates adjusted for covariates at the time of the initial eGFR measurement. However, given the magnitude of the attenuation of these associations after adjustment by the final eGFR, residual confounding is unlikely to alter our conclusions that the final eGFR achieved, rather than retrospective changes in eGFR over the subsequent year, carries the weight of prognostic information.

In conclusion, a drop in eGFR category confirmed by a drop from baseline of  $\geq 25\%$  (a certain drop) is associated with a higher risk of hospitalization for CV events. However, when taking into account the last eGFR, the previous 1-year change



**Figure 16.** Risk of acute myocardial infarction, congestive heart failure, and stroke by 1-year change in kidney function adjusted for covariates at the last measurement among participants aged  $\geq 65$  years. Models were adjusted for age, sex, diabetes, hypertension, socioeconomic status, estimated glomerular filtration rate (eGFR), albuminuria, and history of comorbidities at the last measurement.

in eGFR does not appear to add clinically meaningful information about the risk of future CV events.

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## Disclosures

None.

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