Risk of end-stage renal disease in Japanese patients with chronic kidney disease increases proportionately to decline in estimated glomerular filtration rate

Kunihiro Matsushita[1,2], Jingsha Chen[1,2], Yingying Sang[1,2], Shoshana H. Ballew[1,2], Ryutaro Shimazaki[3], Masafumi Fukagawa[4], Enyu Imai[5], Josef Coresh[1,2] and Akira Hishida[6]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, Maryland, USA; [3]R&D Division, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; [4]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; [5]Nakayamadera Imai Clinic, Takarazuka, Japan; and [6]Yaizu City Hospital, Yaizu, Japan

Predominantly based on North American and European studies, 30% to 40% declines in estimated glomerular filtration rate (eGFR) over a few years are strongly associated with the risk of end-stage renal disease (ESRD) and have been proposed as surrogate endpoints of ESRD for clinical research. However, this association has not been systematically quantified in Asian populations. To do this we studied adult Japanese patients with baseline eGFR 10–59 ml/min/1.73m^2. Changes in eGFR from baseline measured by centrally assessed serum creatinine were linked to subsequent ESRD in 2410 patients after one year and in 2079 patients after year 2. After year 1, 1.4% experienced a 53% decrease in eGFR (equivalent to doubling of serum creatinine), whereas 4.3% and 9.7% had eGFR decrease of 40% or 30% or more, respectively. The corresponding numbers after 2 years were 4.2%, 10.9%, and 19.3%, respectively. After year 1 baseline period, 498 patients developed ESRD over a median follow-up of 2.9 years (365 ESRD cases over a median follow-up of 2 years after year 2). In year 1, after accounting for potential confounders, a strong linear association was found between eGFR declines and subsequent ESRD, with adjusted hazard ratios of 20.7 (95% confidence interval 14.3-30.1) for a 53% decrease, 9.6 (7.4–12.5) for a 40% decrease, and 5.3 (4.1–6.9) for a 30% decrease compared to no change. Corresponding hazard ratios for year two analysis were 17.3 (11.8–25.3), 6.5 (4.7–9.1), and 3.1 (2.2–4.4), respectively. The associations were consistent across demographics and kidney diseases. Thus, 30% to 40% declines in eGFR are strongly associated with the risk of ESRD in Japanese patients with reduced eGFR, broadening global implications as a surrogate endpoint in clinical research.

Kidney International (2016) **90,** 1109–1114; http://dx.doi.org/10.1016/j.kint.2016.08.003

Correspondence: *K. Matsushita, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 E. Monument Street, Suite 2-600, Baltimore, MD 21287, USA. E-mail: kmatsus5@jhmi.edu*

Received 23 March 2016; revised 28 July 2016; accepted 4 August 2016; published online 22 September 2016

KEYWORDS: chronic kidney disease progression; end-stage renal disease; glomerular filtration rate; prospective study; surrogate endpoints

In 2014, an international collaborative working group sponsored by the US National Kidney Foundation (NKF) and the US Food and Drug Administration (FDA) published a series of papers exploring the possibility of using declines in estimated glomerular filtration rate (eGFR) smaller than what has been accepted (i.e., halving corresponding to doubling of serum creatinine) as surrogate endpoints of end-stage renal disease (ESRD) for clinical trials.[1–4] Overall, the investigations of the NKF-FDA working group support 30% to 40% declines in eGFR over 2 to 3 years as a surrogate endpoint.[5] Such lesser declines of eGFR as a surrogate for ESRD have been positively acknowledged from investigators and drug regulatory agencies.[6–8]

However, those papers from the NKF-FDA working group predominantly relied on data from Europe and North America.[1–4] For example, the flagship paper using data from the Chronic Kidney Disease (CKD) Prognosis Consortium included only 0.5% Asians out of the entire study population at risk of ESRD.[1] There are substantial regional differences in the prevalence and incidence of ESRD,[9] and several East Asian countries or regions (Taiwan, Japan, urban China, and South Korea) are ranked among the top 10 of the world.[9] Higher rates of CKD progression in Asians than in whites are confirmed among residents in the US.[10] Also, the pattern of kidney disease is unique in Asians (e.g., higher prevalence of IgA nephropathy).[11] For those reasons, it would be useful to validate in Asians the risk relationship of lesser declines in eGFR and subsequent risk of ESRD, as they are globally accepted as a surrogate endpoint in clinical practice and research. Such an investigation will be particularly useful for regulatory agencies in Asia and international trials including Asian countries or regions. In this context, recently a study from Japan tackled this study question, but it included a small number of patients with approximately 80 events of ESRD and had a retrospective design, limiting its generalizability.[12] Therefore, we quantify the association of percentage

changes in eGFR over time and the subsequent risk of ESRD using data from a nationwide cohort of patients with CKD in Japan, the Chronic Kidney Disease Japan Cohort (CKD-JAC).

RESULTS

Of the 2410 participants with repeated eGFR in 1 year, 1.4% (34 participants) experienced –53% change in eGFR (equivalent to doubling of serum creatinine using a validated Japanese equation[13]) during the 1-year baseline period, whereas 4.3% (104 participants) and 9.7% (233 participants) had eGFR change ≤–40% and ≤–30%, respectively (Figure 1a). The corresponding numbers for 2079 participants in the 2-year baseline period were 4.2% (87 participants), 10.9% (227 participants), and 19.3% (401 participants), respectively (Figure 1b). Overall, the average change in eGFR was –7% (SD 19%) in the 1-year and –13% (SD 22%) in the 2-year baseline periods. As compared to participants with stable eGFR (> –30% to 0% change) over time, those with eGFR changes ≤ –30% were more likely to be female, current smokers, and diabetic and to have higher levels of total cholesterol, higher blood pressure, a history of cardiovascular disease, lower eGFR, higher levels of albuminuria, and lower hemoglobin concentrations at baseline (Supplementary Table S1 for 1-year analysis and Table 1 for 2-year analysis).

Of the 2410 participants in the 1-year analysis, 498 participants (20.7%) developed ESRD during a median follow-up of 2.9 years after the 1-year baseline period (59 died before reaching ESRD). In the 2-year analysis, 365 ESRD cases (17.6%) were observed during a median follow-up of 2.0 years among 2079 participants (31 deaths before ESRD). As shown in Figure 2, eGFR decline over the 1-year and 2-year baseline periods was strongly associated with subsequent risk of ESRD. Specifically, –53% change in eGFR corresponding to doubling of serum creatinine over 1 and 2 years was associated with a 21- and a 17-fold higher risk of ESRD (adjusted hazard ratio 20.72 [95% CI, 14.27–30.09] and 17.27 [11.80–25.30]) compared to no change in eGFR, respectively. Although not as strong as the –53% eGFR change, a –40% change and a –30% change were also strongly associated with ESRD risk (adjusted hazard ratio 9.61 [95% CI, 7.42–12.46] and 5.32 [4.14–6.85] for 1-year analysis and 6.53 [4.70–9.05] and 3.09 [2.15–4.42] for 2-year analysis, respectively) (Figure 2). We observed an increased risk of ESRD according to an increase in eGFR in the 1-year but not necessarily in the 2-year analysis.

We conducted several sensitivity analyses to assess the robustness of our findings. First, further adjustment for albuminuria and hemoglobin did not alter the results (Supplementary Figure S1). Second, we performed subgroup analysis by age and gender (Supplementary Figures S2 and S3). Although the association was significantly stronger in men than in women (P for interaction < 0.001), overall, changes in eGFR were qualitatively consistently associated with ESRD risk in all subgroups tested. Thirdly, we stratified by causes of CKD and generally observed similar patterns (Supplementary Figure S4). Finally, we repeated the analyses using the creatinine-based CKD-EPI equation and observed similar results (Supplementary Figure S5).

In terms of absolute risk, the sharp risk gradient according to eGFR declines translated to high predicted risk of subsequent ESRD over 1 to 3 years after the baseline period (Supplementary Figure S6 and Figure 3), particularly when baseline eGFR was low. For example, when the baseline eGFR was 50 ml/min/1.73m^2 at GFR stage 3A, the 3-year subsequent predicted risk of ESRD was approximately 4% to 5% even for 1-year and 2-year change in eGFR of –53%, whereas when baseline eGFR was 35 ml/min/1.73m^2 at GFR stage 3B, the risk was 35% and 30% for –53% change, 19% and 14% for –40% change, and 11% and 7.0% for –30% change, respectively. In case of a baseline eGFR of 25 ml/min/1.73m^2 at GFR stage 4, the corresponding 3-year ESRD risk was 86%,

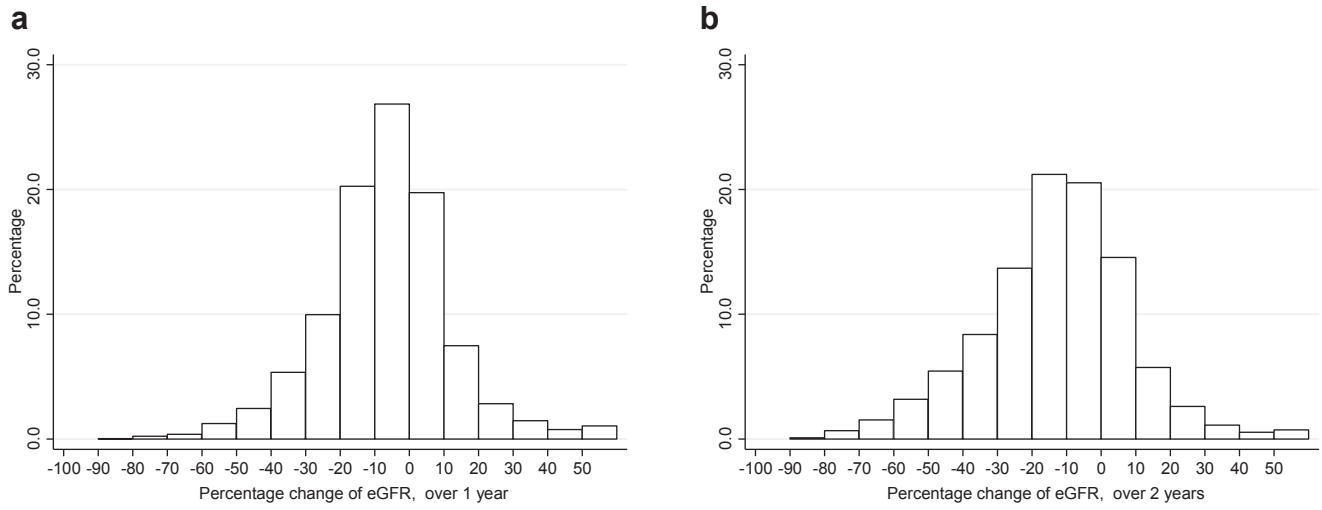

Figure 1 | Distribution of percentage changes in eGFR during (a) 1-year and (b) 2-year baseline periods. Percentage change in eGFR was calculated as (last eGFR at baseline period – first available eGFR)/(first available eGFR) * 100.