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COMMENT

# No "U-shaped" associations of estimated glomerular filtration rate with adverse cardiovascular outcomes in patients with primary aldosteronism

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**Keywords** Cardiovascular disease · Estimated glomerular filtration rate · Glomerular hyperfiltration · Primary aldosteronism · 2021 race-free Chronic Kidney Disease Epidemiology Collaboration eGFR equation

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Primary aldosteronism (PA) is a common type of secondary hypertension that causes comparatively more severe injury to the heart, brain, and kidneys, relative to essential hypertension [1, 2]. The mechanisms by which PA causes chronic kidney disease are directly associated with aldosterone-induced activation of mineralocorticoid receptors (MRs). This activation increases the circulating plasma volume because of increased urinary sodium reabsorption in renal cortical collecting duct cells, while inducing vascular remodeling and fibrosis of the renal vasculature, interstitial cells, and glomerular podocytes. MR activation also contributes to glomerular hyperfiltration via constriction of efferent arterioles and vasodilation of afferent arterioles [3]. A decreased glomerular filtration rate (GFR) is a predictor of cardiovascular disease and mortality in healthy people [4]. The relationship between GFR and the incidence of cardiovascular events in patients with PA is unknown, although there have been reports of altered cardiovascular event incidence and renal prognosis depending on the choice of treatment and the post-treatment renin concentration [5, 6].

Various methods may be used to evaluate the GFR, but the estimated GFR (eGFR)—based on a formula involving the serum creatinine concentration (SCr), age, and sex—is often used because of its simplicity. The National Kidney Foundation–American Society of Nephrology Task Force recently recommended the use of the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration eGFR (2021 race-free eGFR equation) to calculate the eGFR [7]. The 2021 race-free eGFR equation, which uses both SCr and the serum cystatin concentration (SCys), is expected to produce fewer race-based differences than a formula that uses only SCr or SCys.

Hemodynamic change-related glomerular hyperfiltration may mask actual kidney dysfunction. Because no studies have shown associations of baseline kidney function with long-term cardiovascular outcomes, Lai et al. [8] recently investigated whether the calculated baseline 2021 race-free eGFR could predict new-onset composite cardiovascular events among patients with PA (total death, non-fatal myocardial infarction, and coronary revascularization events) in the Taiwan PA Investigation registry. This observational cohort study enrolled 760 coronary artery disease-naïve patients who had been diagnosed with PA. Multivariable Cox proportional hazards analysis showed that baseline 2021 race-free eGFR was an independent cardiovascular event factor in patients with PA (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.97–0.99). Patients with PA who had a baseline 2021 race-free eGFR of <85 mL/min/1.72 $m^2$ also exhibited significantly higher incidences of composite cardiovascular events (HR, 2.39; 95% CI, 1.16–4.93), all-cause mortality (HR, 4.63; 95% CI, 1.59–13.46), and adverse kidney events (subdistribution HR, 5.96; 95% CI, 3.69–9.62, with mortality as a competing risk). This study was the first to use the baseline 2021 race-free eGFR for assessment of renal function in patients with PA, along with subsequent event incidence. An intriguing finding was that a higher baseline 2021 race-free eGFR was associated with a lower HR of composite cardiovascular events. Renal hyperfiltration is a sign of high glomerular overload [9], which leads to poor renal outcomes in healthy individuals and patients with essential hypertension. In non-diabetic patients, there are "U-shaped" associations between eGFR and adverse cardiovascular

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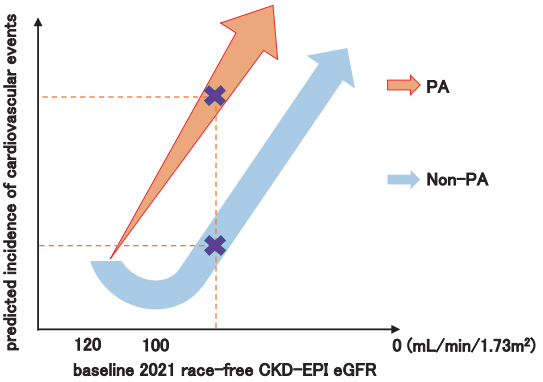


**Fig. 1** Relationship between baseline 2021 race-free CKD-EPI eGFR and predicted cardiovascular event incidence in patients with PA. eGFR, estimated glomerular filtration rate; PA primary aldosteronism; CKD-EPI Chronic Kidney Disease Epidemiology Collaboration

outcomes. One study showed that a baseline eGFR of 100 mL/min/1.73 $m^2$ was associated with the lowest risks of all-cause mortality and cardiovascular death, whereas baseline eGFRs of <100 and >100 mL/min/1.73 $m^2$ were associated with increasing levels of risk [10]. In contrast, Lai et al. [8] showed no "U-shaped" associations between baseline eGFR and predicted cardiovascular outcomes in patients with PA. Instead, they found that among patients with PA, a higher eGFR was associated with a lower predicted cardiovascular risk; the greatest risk was associated with an eGFR of <85 mL/min/1.73 $m^2$. This result is clearly inconsistent with previous reports. Based on these results, we suspect that most patients with PA initially exhibited a hyperfiltration state. The better prognosis for cardiovascular events in patients with a baseline 2021 race-free eGFR of ≥100 mL/min/1.73 $m^2$ suggests that patients with a baseline 2021 race-free eGFR of 90–100 mL/min/1.73 $m^2$ already had a reduced GFR secondary to progressive renal impairment (Fig. 1). Based on this assumption, the management of patients with PA should include the expectation that renal or vascular damage has substantially progressed at the time of PA diagnosis. National guidelines recommend the treatment of PA with MR antagonists (MRAs) for bilateral PA and adrenalectomy for unilateral PA [11, 12]. Adrenalectomy is reportedly superior to MRA therapy in patients with unilateral PA [13]. Adrenalectomy should be performed immediately; however, if a waiting period is required before surgery, MRA therapy should be initiated first. In addition to spironolactone and eplerenone, esaxerenone (a non-steroidal MRA) is currently used in Japan. Spironolactone reportedly decreases urinary albumin excretion in patients with PA [14]; esaxerenone also decreases the N-terminal pro-brain natriuretic peptide concentration in addition to urinary albumin excretion and improves quality of life [15].

The study by Lai et al. [8] had several strengths and limitations. First, it was unique in terms of investigating whether baseline eGFR is associated with long-term cardiovascular outcomes among patients with PA through use of the 2021 race-free eGFR equation. The actual renal function in patients with PA may be worse than it appears because MR activation-mediated glomerular hyperfiltration may produce a pathologically "normal" baseline eGFR. However, Lai et al. [8] showed that a higher eGFR was associated with a lower predicted cardiovascular risk. Second, as the authors mentioned, the validation of these findings will require investigations of whether the baseline and follow-up urine albumin/creatinine ratios are associated with the eGFR. Third, it may be interesting to investigate whether biomarkers of MR activity are associated with the eGFR in a future study. Such biomarkers may include the urine sodium/potassium ratio, plasma renin activity (concentration), and urinary exosomes. Fourth, although the baseline 2021 race-free eGFR can be calculated with a small margin of error for various races, future studies should focus on other races. Fifth, among patients with a high baseline eGFR, glomerular hyperfiltration hinders identification of patients with truly normal renal function and patients with "apparently normal" renal function. To distinguish these two subgroups of patients with a high baseline eGFR, it may be helpful to measure changes in albuminuria or proteinuria: few changes will be present in patients with truly normal renal function, but a significant reduction will be present in patients with "apparently normal" renal function. Sixth, the use of this equation is costly because it requires simultaneous measurement of SCr and SCys. Despite these limitations, the study demonstrated the unique finding that there are no "U-shaped" associations of baseline eGFR with cardiovascular outcomes, and the greatest risk is associated with an eGFR of <85 mL/min/1.73 $m^2$, among Taiwanese patients with PA.

## Compliance with ethical standards

**Conflict of interest** HS has honorarium from Daiichi-Sankyo Company, Bayer, Mochida Pharmaceuticals, Astrazeneca, Novartis Pharma, and Astellas. HS also received scholarship from Chugai and Bayer.

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