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Recent Trends of the Relationship between CKD and SGLT2-I Agent

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Abstract

Recent topics for CKD and SGLT2-i are described. From DAPA-CKD trial, renal function decline was slower for cases of initial dip ≥10% than those of <10%. Then, initial dip ≥10% seems a surrogate for beneficial kidney prognosis. From ADVANCE study, eGFR and urinary albumin-to-creatinine ratio (UACR) show the risk of cardiovascular and renal events. The hazard ratio (HR) of cardiovascular event was 2.48 for 10-fold elevation of UACR and 2.20 for halving of baseline eGFR. HR of cardiovascular death was 1.00, 1.32, 2.08 for diabetes complications in G1, G3a, G3B as each eGFR of 90-104, 45-59, 30-44 mL/min/1.73m^2, respectively.

Keywords: DAPA-CKD; Initial dip; ADVANCE; eGFR; Urinary albumin-to-creatinine ratio (UACR)

Commentary Article

Concerning the initial dip of eGFR, impressive findings were reported from a post hoc analysis of the DAPA-CKD trial [1]. The long-term renal function decline was slower for patients with initial dip ≥10% than that with initial dip <10%. Then, initial dip ≥10% seems to be a surrogate for beneficial long-term kidney prognosis. For elderly people with CKD, geriatric evaluation would be adequate before decision making for kidney replacement. However, implementation has been lacking in routine manner [2]. Geriatric assessment was performed in 191 cases, in which most relevant instruments showed Montreal Cognitive Assessment (MCA) and Clinical Frailty Score (CFS) [3].

When dapagliflozin is provided to CKD patients, the initial eGFR dip has been observed. A meaningful study was conducted for analyzing the relationships between initial eGFR dip after SGLT2-i and morphometrical and histopathological findings of renal biopsy [4]. This study included 60 CKD cases as average age 52 years, male 72%, median eGFR 52.0 ml/min per 1.73 m2, median urinary albumin-to-creatinine ratio (UACR) 1.13 g/day. As a result, the CKD cases with larger glomerular volume showed higher prevalence of ≥10% of initial eGFR dip in comparison with baseline. This investigation would be the first study for clarifying the relationship between initial eGFR and pathological findings.

For decade, clinical progress of NAFLD has been crucial problem, and close attention has observed whether SGLT2-i may contribute the prevention and treatment of NAFLD or not. Recent research has shown efficacy for evidence of external and animal experiments [5]. Concerning the beneficial efficacy of SGLT2-i on renal function, molecular mechanisms were studied using streptozotocin (STZ)-induced mouse [6]. As a result, canagliflozin existence restored subcellular localization of SGLT2, integrin beta 1, 78-kDa glucose-regulated protein (GRP78) and inhibited fibrosis and epithelial mesenchymal transition (EMT) in diabetic kidney. For non-diabetic CKD, canagliflozin increased endoplasmic reticulum (ER) robustness by preventing ER impaired response and keeping sarco/ ER Ca2+-ATPase (SERCA) activity, leading to tubular protection.

For Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study, clinical effect of routine BP lowering on adverse outcomes in type 2 diabetes (T2D) was investigated. Successive study was conducted to examine the influence of eGFR and UACR for the risk for cardiovascular and renal events for 10,640 cases [7]. For 4.3 years period in average, there were cardiovascular events (8.8%) and renal events (1.0%). The hazard ratio (HR) of CV event was 2.48 for 10-fold elevation of UACR and 2.20 for

halving of baseline eGFR. Cases with both eGFR <60 mg/min/1.73m^2 and UACR >300 mg/g showed 3.2-fold increased risk of CV events and 22.2-fold higher risk for renal events, in comparison with cases of no these risk factors. Consequently, the intervention of treatment from early stages would be required.

CKD has become the risk for dialysis and future cardiovascular disease. Hazard ratio (HR) of cardiovascular death was 1.00, 1.32, 2.08 for diabetes complications in G1 (control), G3a, G3B as each eGFR value of 90-104, 45-59, 30-44 mL/min/1.73m^2, respectively [8]. Similarly, significant difference was present as 1.00, 1.48, 2.10 for those patients without diabetes. Thus, decreased eGFR is also associated with an increased risk of cardiovascular death, which is regardless of the presence of diabetes or not.

For the changes in eGFR, meaningful standard has been observed for the decline degree for some years. One surrogate endpoint for renal disease progression was the rate of decline in eGFR slope >0.5-1.0 mL/min/1.73 m^2/year [9]. The United State Food and Drug Administration (FDA) and also European Medicines Agency (EMA) have considered about 30-40% GFR decline that is a surrogate end point for renal failure in the cases of clinical trials under adequate conditions. National Kidney Foundation (NKF) has sponsored the workshop with FDA and EMA, and evaluated GFR and/or albuminuria for candidate of surrogate end points. Regarding cohort studies, eGFR slope and UACR values have become strong and consistent factors for clinical outcome of renal disease progression. As the candidate surrogate, the risk for clinical outcome showed the consistency for cohorts and trials. As a result, 30% decrease of UACR or 0.5-1.0 decrease/year of eGFR slope showed the relationship with hazard ratio (HR) of ~0.7 among the obtained outcome in several studies.

The latest report was found from the Japan Chronic Kidney Disease Database (J-CKD-DB). Using J-CKD-DB, eGFR slope was studied for 1-, 2- and 3-year for CKD cases with ≥30 mL/min/1.73 m^2 of baseline eGFR (n=7768 for 1-year) [10]. The outcome was set as ESKD (CKD stage G5 or dialysis initiation). The association of eGFR slope and the sub-distribution hazard ratio (SHR) was calculated by Fine-Gray proportional hazard regression model. As a result, a trend toward lower ESKD risk was found as lower eGFR slope. In comparison with 1-year slope, smaller variation was observed for 2- and 3- year slope and remarkable SHR decrease were recognized. Consequently, appropriate period seemed to be 2-3 years period for evaluating eGFR slope.

EMPA-KIDNEY studies evaluated efficacy of empagliflozin vs placebo in 6609 CKD cases, in which 612 cases were Japanese. In post-hoc analysis, clinical effect was compared for Japan vs. non-Japan regions. As a result, Japanese cases showed higher albuminuria and eGFR values than those of others. During 2-year follow-up in median, primary outcome was found in 13.1% of empagliflozin group and 16.9% in placebo group, where HR was 0.72 [11]. The results were similar in non-Japan regions. Safety outcomes were observed in both groups. Consequently, empagliflozin safely decreased the risk of cardiovascular death or renal disease progression for CKD patients in Japan and other regions.

Comparing the groups from G1 (>90) to G3 (30-59) and G5 (<15 mL/min/1.73m^2), the obtained data were found. As albuminuria increases from normal to trace to overt, CVD mortality increases from 1.0 to 5.9 times, and renal events increases from 1.0 to 22.2 times. Worsening of these factors will elevate mortality, ESRD, and cardiovascular risk. Consequently, it would be crucial to reduce albuminuria and proteinuria as well as to suppress eGFR slope for preventing the exacerbation of kidney disease [12].

In summary, recent topics for renal disease and SGLT2-i were described. The slope of eGFR reduction would be a crucial biomarker, and this article will be hopefully a beneficial reference for renal practice.

Conflict of Interest

The authors declare no conflict of interest.

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