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Beneficial Pharmacotherapy of Metformin for Diabetic Kidney Disease (DKD) with Decreased eGFR

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Abstract

The American Diabetes Association (ADA) has presented the standard of care (SoC)-2025 in January, 2025. Among oral hypoglycemic agents (OHAs), recent topics clinical effect of metformin, which has been the first-line agent for long years. When eGFR becomes below 30 mL/min/1.73m^2, metformin has been recommended to be discontinued so far. Recent report showed the comparison of continuing or discontinued metformin when the case enters stage 4 of chronic kidney disease (CKD). As a result, discontinued group showed lower 3-year survival as 63.7% *vs* 70.5%, higher all-cause mortality 1.34, and similar hazard ratio (HR) 1.05 of major adverse cardiac event (MACE).

Keywords: Oral hypoglycemic agent (OHA); Metformin; Chronic kidney disease (CKD); Major adverse cardiac event (MACE); Kidney Disease Improving Global Outcomes (KDIGO)

Commentary Article

In January 1, 2025, the standard of care (SoC)-2025 has been presented by American Diabetes Association (ADA) [1]. It has been the cornerstone of diabetic diagnosis and treatment for decades. In the chapter of pharmacotherapy of the diabetes, various types of oral hypoglycemic agents (OHAs) have been found [2]. Among them, first-line drug therapy includes sodium-glucose cotransporter 2 inhibitor (SGLT2i) (initiate if estimated glomerular filtration rate (eGFR) is >20 mL/min/1.73m^2; continue until dialysis or transplant), metformin (if eGFR >30 mL/min/1.73m^2), renin-angiotensin system (RAS) inhibitor at maximum tolerated dose (if albuminuria and/or hypertension) and moderate-or high-intensity statin.

In order to decrease cardiovascular disease (CVD) mortality and morbidity in type 2 diabetes (T2D) cases with high risk for CVD, two important agents of SGLT2i and/or glucagon-like peptide-1 receptor agonist (GLP-1RA) would be considered [3]. Other oral hypoglycemic agents (OHAs) may remain necessary for control T2D, whereas they do not show cardiovascular effects. Although both agents have attracted attention for practical benefit, metformin has been re-evaluated for its clinical efficacy that has been the first-line agent for long years.

The selection of glucose-lowering medications for people with T2D and established chronic kidney disease (CKD) is made with special considerations including limitations to available medications when eGFR is diminished and there is a desire to mitigate risks of CKD progression, CVD, and hypoglycemia [4,5]. Medication dosing may require modification with eGFR <60 mL/min/1.73^2 [6].

Figure 1 shows the ADA and Kidney Disease: Improving Global Outcomes (KDIGO) consensus recommendation algorithm for medications in people with diabetes and CKD [2].

Concerning the clinical effect of diabetic kidney disease (DKD), a comparative study was conducted for OHAs of DPP4i and SGLT2i [7]. The protocol included the investigation of Taiwan's National Health Insurance Research Database for SGLT-2is (n = 1524) and DPP-4is (n = 6005). As a result, SGLT-2i users showed reduced risk of composite renal endpoint (HR 0.16) compared with DPP-4i users. Furthermore, they revealed prolonged time to 50% or higher

eGFR decrease (HR 0.17), renal failure (HR 0.14), and less renal death (HR 0.10). SGLT-2i users showed better composite CV outcome (HR 0.74), lower stroke risk (HR 0.76), and less hospitalization for heart failure (HR 0.68). Thus, superior cardiorenal benefits of SGLT2is were found when compared with DPP-4is for DKD cases.

A retrospective cohort study showed CKD progression for T2D patients. The protocol included 1003 cases followed for up to 11 years, and CKD cases with stages 3-5 were found for 388 cases [8]. The cumulative incidence was 38.7% for 38 cases per 1000 person-years. High intensity statin users seemed to develop CKD stage 3-5 rather than low/moderate intensity users and no statin users (44.3%, 37.9%, 30.9%, respectively). On the other hand, biguanide users showed decreased probability of CKD progression as 37.9% vs 52.8%, p=0.001). Further, insulin users showed higher risk as 54.6% *vs* 34.1%, p<0.001).

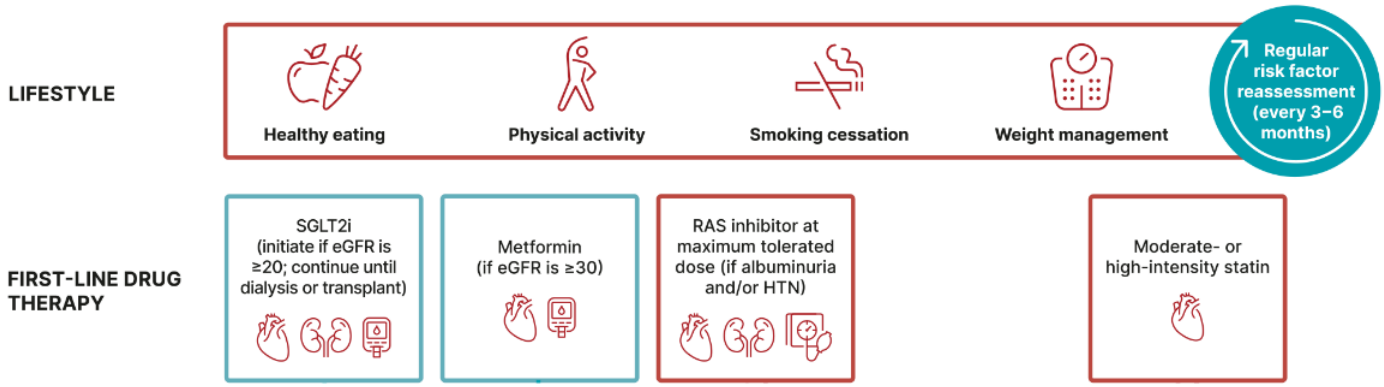

Figure 1: *Holistic approach for improving outcomes for diabetes and CKD.*

A comparative investigation held in Hong Kong for discontinued-Met group and continued-Met group for DKD patients with stage 4 [9]. The protocol included 33586 cases with metformin prescription and decreased eGFR less than < 30 ml/min/1.73 m^2. Among them, 7500 (22.3%) cases discontinued metformin within 6 months, but 26,086 (77.7%) continued metformin. During follow-up 3.8 years in median, incidents occurred as 16.4% in major adverse cardiac event (MACE), 30.1% in end-stage kidney disease (ESKD), 7.1% in cancer, respectively, and 44.4% died. In comparison with the continued-Met group, the discontinued-Met group showed higher risk of MACE as 1.40 of Hazard Ratio (HR), ESKD (HR 1.52), and death (HR 1.22). There was no relationship for cancer (HR 0.93). The discontinued-Met group showed higher HbA1c change at 6 months compared with continued-Met group as +0.5% *vs* +0.2%, respectively. For a separate register-based study (n=3235), no relationship was found for metformin use and lactic acidosis risk (HR 0.94).

For CKD patients, metformin may give long-term benefits associated with the first-line agent for diabetes. However, eGFR should be assessed regularly, in order to minimize the risk of metformin accumulation. When eGFR becomes below 30 mL/min/1.73m^2, metformin has been recommended to be discontinued so far [10]. This notion was initially based on the data regarding increased lactic acidosis risk in phenformin use [11]. Metformin accumulation may elevate the risk of lactic acidosis. However, recent research has re-evaluated the previous method of metformin for CKD and DKD.

Metformin has been prevalent worldwide for T2D treatment. It is readily affordable, available and has a good safety profile [12].

Its adverse effects include GI-tract disturbances and vitamin B_{12} deficiency, which are both easily managed. Metformin-associated lactic acidosis has been very rarely observed [13]. From a basic point of view, it can primarily impart its therapeutic actions through the activation of adenosine monophosphate (AMP)-activated protein kinase. It subsequently inactivates the molecular target of rapamycin and also its postulated downstream fibrogenic effects on the kidney [14]. Consequently, metformin may improve outcomes in CKD as well as improving blood glucose control. Since metformin is predominantly excreted unchanged in the urine, the risk of accumulation and adverse events would be found when renal function is impaired [13]. Consequently, it has been avoided in later CKD stages so far associated with few data in stage 3-4.

Impressive results were found from the latest report on DKD and metformin administration. The research was 10-year Scottish nationwide observational cohort study with all T2D patients in stage 4 CKD (eGFR < 30mL/min/1.73m^2) [15]. Among 371,742 Scottish T2D cases, 4,278 showed prevalent metformin with incident CKD stage 4. As clinical situation, 1,713 (40.1%) cases stopped metformin within 6 month of entering stage 4. In comparison with cases of continuing metformin, stopped metformin cases showed lower 3-year survival (63.7% *vs* 70.5%) with HR 1.26, and MACE incidence showed similarity (HR 1.05). By marginal structural model analyses, higher risk of all-cause mortality and similar risk of MACE was observed for stopped *vs* continued metformin group, as mortality HR 1.34, and MACE HR

1.04. Consequently, continued metformin use may be adequate when eGFR falls under 30mL/min/1.73m^2. A randomized controlled trial (RCT) will be required for confirming these findings.

In summary, this article described recent topics concerning the first-line agent as metformin. It has been avoided when diabetic patient shows decreased eGFR to 30 mL/min/1.73m^2. However, several beneficial effects have been found for stage 4 nephropathy. Consequently, further evaluation in the future will be expected.

Conflict of Interest

The authors declare no conflict of interest.

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