BANTAO Journal 2021; 19(2): 65-66

BJ

BANTAO Journal

Editorial

SGLT-2 Inhibitors and GLP-1 Receptor Agonists May Prevent Cardiovascular and Chronic Kidney Disease Progression in Patients Regardless the Diabetic Status

Goce Spasovski[1], Merita Rroji[2], Goce Hristov[3], Natasha Nedevska[4], and Irena Rambabova Bushletikj[1]

[1]Department for Nephrology, Medical Faculty, University Sts. Cyril and Methodius, Skopje, N. Macedonia, [2]Department for Nephrology, University of Tirana, Tirana, Albania [3]Department for Internal medicine and Diabetes – General Public Hospital Strumica, Strumica, N. Macedonia, [4]Department for Endocrinology and Diabetes – General Public Hospital "8th September" Skopje, N. Macedonia

The most frequently developed complication of long-term diabetes is cardiovascular (CVD) and chronic kidey disease (CKD). The CVD prevalence in diabetic patients is around 32.2% [1], with a two-fold increased mortality risk compared to those without diabetes [2]. The question remains about the proportion of patients with type 2 diabetes (T2D) at high risk of mortality that could probably achieve the most significant benefit from an aggressive control of the modifiable risk facors and expectedly newer glucose-lowering agents.

Nowadays, two classes of anti-hyperglycemic drugs may reduce CV risk in patients with T2D [sodium-gluose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA)]. Empaliflozin treatment (10 mg) for around two years reduced the risk of a composite of CV death or hospitalization for heart failure (HF) by 21% [3]. FDA approved dapagliflozin and empagliflozin as drugs reducing the risk of CV death or hospitalization for HF in patients regardless of their diabetic status [4,5]. In addition, despite the similar benefit (RR 12 to 14%) of the two drugs on major cardiovascular events (MACE) in T2D patients, only GLP-1RA reduces the risk of stroke. Conversely, the hospitalization rate for HF in SGLT-2i treated patients is around threefold as compared to GLP-1RA treatment. However, in cases where SGLT-2i are contraindicated or not tolerated, GLP-1RA may exert the same effect on HF hospitalization. As for kidney outcomes, both drugs have shown similar protective cardiorenal effects. In a recent retrospective study, both drugs reduced the 10-year risk for CVD in T2D patients in primary cardiovascular prevention [6], while SGLT-2i had a more significant cardioprotective benefit for secondary prevention [7]. Nevertheless, the optimal clinical management of T2D seems not clear yet mainly because of the panoply of anti-glycemic targets and variety of existing drugs for the first and consequent drug choice, risk factors graduation for prevention of vascular complications, and achieved treatment outcomes (surrogate vs. clinical).

Additionally, the existing and new treatment guidelines releases generate more confusion than help in improving the guidance among clinicians [8]. Given that all available combinations in treatment could not be feasible and treatment algorithms could not be evidence-based lacking in comparative studies, the confusion among physicians leads towards clinical inertia for these drugs [8,9]. Hence, there is a need for coordinated action for the appropriate treatment of T2D patients with CVD and CKD with an SGLT-2 inhibitor or GLP-1RA. This is especially important in view of the recent survey about the declining glycemic control and increased number of vascular diabetic complications in the last decade [10,11].

In conclusion, SGLT-2i and GLP-1RA reduce CVD and CKD risks while controlling glycemia in patients with T2D. On top of it, SGLT-2i may be beneficial even in nondiabetic patients with HF with or without presserved ejection fraction introducing these therapies in patients at risk or with established CV or CKD. Finally, the medicare system should incorporate these treatment possibilities as regular support through the health insurance system for both (with or without T2D) patient groups at risk or with established CVD and CKD.

In light of the new evidence, we may say a new perspective might be opened for treatment of CKD that postpone disease progression and development of end-stage kidney disease and the need for renal replacement therapy. This effect certainly goes along with cardiovascular disease prevention and prolonged survival of CKD patients. In the last two decades, mainstream therapy for preventing CKD progression in patients with and without T2D was either angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blo-

Correspondence to: Goce Spasovski, University Clinic for Nephrology, Vodnjanska 17, 1000 Skopje, R. N. Macedonia; E-mail: spasovski.goce@gmail.com

ckers (ARB). However, the holistic treatment approach would also include a decreased risk of all-cause mortality in these CKD patients regardless of the presence of diabetes as a major risk factor.

Hence, in a couple of randomized, placebo-controlled studies in patients with T2D, in addition to the signifycant reduction of the cardiovascular risk, SGLT2 inhibitors improved the renal outcomes (reduction of the kidney function, worsening of albuminuria, stage kidney disease (ESKD) or death from renal cause) in comparison with placebo [12-14]. Regardless of the improvements achieved in these studies, they were not designed to evaluate treatment benefits in CKD patients consisting of a minor proportion of patients with eGFR of ≤60 mL/min/1.73 m2.

So, expectedly, the recent evidence showed a positive effect of SGLT2i in the designated kidney outcome trials in CKD patients with T2D (CREDENCE) [15], regardless of T2D status (DAPA-CKD) [16]. Here, canagliflozin has achieved significantly reduced risk of CKD progression in T2D patients, the same as reported for Dapagliflozin (in patients with or without T2D) with additional effect on the reduced all-cause mortality risk. Recently, among a wide range of patients with CKD at risk for the disease progression, EMPA-KIDNEY trial showed that empagliflozin treatment led to a lower risk of CKD progression or death from cardiovascular causes compared to placebo [17]. Hence, a new hope on the horizon appeared in view of the SGLT2i treatment of early CKD patients with or without diabetes. Based on the findings of the studies mentioned above, the Food and Drug Administration (FDA) has expanded the approval of canagliflozin for T2D patients with diabetic nephropathy (albuminuria ≥300 mg/day and an eGFR ≥30 mL/min/1.73 m2 [18], and for dapagliflozin in patients with CKD with an eGFR ≥25 mL/min/1.73 m2 at risk of CKD progression [19].

In conclusion, and considering the presented evidence, our Balkan nephrological community should be aware of this new added value in the retardation of CKD progression in patients with or without diabetes. We should also make sensible our authorities and health providers for the cost-efficacy of the SGLT2i in the management of CKD patients. Finally, this new class of renoprotection should be gradually implemented into our clinical practice for the benefit of our patients and the healthcare system.

Conflict of interest statement. None declared.

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