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Novel antidiabetic drugs in diabetic kidney disease accompanying type 2 diabetes — a minireview

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Abstract: Intensive hypoglycemic treatment is the strongest preventive strategy against the development of microvascular complications of type 2 diabetes (T2DM), including diabetic nephropathy. However, some antidiabetic drugs, i.e. sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA) have an additional renoprotective effect beyond glucose control by itself. Similar, both SGLT-2i and GLP1-RA have been demonstrated to decrease the risk of adverse cardiovascular (CV) events in CV outcome trials. Nevertheless, there are relevant differences in CV and renal effects of SGLT-2i and GLP1-RA. First, SGLT2i reduced the incidence and progression of albuminuria and prevented loss of kidney function, while predominant renal benefits of GLP1-RA were driven by albuminuria outcomes. Second, the risk of heart failure (HF) hospitalizations decreased on SGLT2i but not on GLP1-RA, which gives priority to SGLT2i in T2DM and HF, especially with depressed EF. Third, either GLP1-RA (reducing predominantly atherosclerosis-dependent events) or SGLT-2i, should be used in T2DM and established atherosclerotic CV disease (ASCVD) or other indicators of high CV risk. In this review, we have briefly compared clinical practice guidelines of the American Diabetes Association (2020 and 2021 versions), Polish Diabetes Association (2020) and the European Society of Cardiology/European Association for the Study of Diabetes (2019), with a focus on the choice between SGLT-2i and GLP1-RA in patients with diabetic kidney disease.

Keywords: sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, renoprotection, diabetic kidney disease, type 2 diabetes, cardiovascular outcome trials, clinical practice guidelines.

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Diabetic kidney disease (DKD), defined as chronic kidney disease (CKD) attributable to diabetes, affects 20–40% of diabetic patients [1]. Diabetic nephropathy, the best known type of DKD, is one of microvascular complications of diabetes presenting with albuminuria gradually progressing to overt proteinuria and loss of renal function. Obviously, intensive hypoglycemic treatment is the strongest preventive strategy against the development of microvascular complications of T2DM, including DKD, with a lag time of at least 2 years between intensive glucose control and attenuated renal function decline in type 2 diabetes (T2DM) [1]. Nevertheless, some antidiabetic drugs have an additional renoprotective effect irrespective of glucose control.

According to the 2020 version of the guidelines of the American Diabetes Association (ADA) [2], only several antihyperglycemic agents have been labelled as associated with additional renal benefits in T2DM, i.e. slower progression of CKD, extending the well-recognized glucose-lowering effect. These agents included exclusively three sodium-glucose cotransporter-2 inhibitors (SGLT2i) (canagliflozin, empagliflozin and dapagliflozin) and liraglutide, a glucagon-like peptide receptor-1 agonist (GLP1-RA) [2]. The above presented list has recently been extended in the 2021 upgrade of the ADA guidelines [3], released in December 2020. Accordingly, not only liraglutide but also other GLP1-RA, i.e. semaglutide and dulaglutide, are currently labelled as renoprotective, with predominant benefit on renal end points driven by albuminuria outcomes in cardiovascular outcome trials (CVOTs). It is noteworthy that — according to the ADA guidelines [2, 3] — no renal dose adjustment with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 nm^2 is necessary for all these GLP1-RA, in contrast to SGLTi, contraindicated with eGFR below 30–45 mL/min/1.73 m^2.

Various renal outcome measures were used in CVOTs, including progression of albuminuria, a 30–50% decline of eGFR, doubling of serum creatinine, incidence of end-stage renal disease or death from a renal cause. SGLT2i reduced the incidence and progression of albuminuria as well as slowed the loss of eGFR [4], which was maintained upon multivariate adjustment including glycated hemoglobin (HbA1c) down to an eGFR of 30 mL/min/1.73 m^2, as demonstrated in the EMPAREG-OUTCOME, CANVAS, CREDENCE, DAPA-HF and DECLARE-TIMI 28 trials. Importantly, recent results of the DAPA-CKD, DAPA-HF and EMPEROR-Reduced trials have proven the ability of SGLT2i to prevent both loss of renal function and adverse CV events (CV death and heart failure (HF) hospitalizations) in diabetic and non-diabetic patients with either CKD and albuminuria >200 mg/g creatinine [5] or HF with EF <40% [6, 7] irrespective of baseline estimated glomerular filtration rate (eGFR). That the glucose-lowering effect of SGLT2i is attenuated at lower eGFR and may even be lost in non-diabetics [1, 5–7], points into predominantly non-glycemic mechanisms underlying clinical advantages of this drug class. As mentioned earlier, renal benefits of

GLP1-RA were mediated mainly by a lower progression rate of albuminuria, as shown in the LEADER, SUSTAIN-6 and REWIND trials [3, 4].

Since the optimization of renoprotection is of paramount importance in T2DM patients with diabetic nephropathy, SGLT2i should be used in T2DM patients with eGFR ≥30 mL/min/m^2 and albuminuria (defined as albumin-to-creatinine ratio (UACR) ≥30 mg/g creatinine in a random urinary sample [1]), particularly at UACR >300 mg/g creatinine [1–3]. When SGLT2i cannot be used (eGFR <45 mL/min/1.73 m^2 for empagliflozin and canagliflozin or eGFR <30 mL/min/1.73 m^2 for dapagliflozin according to the recent FDA approval [1]) or are not tolerated, GLP1-RA provide an alternative [1, 3]. In patients with DKD without albuminuria and an eGFR of 30–60 mL/min/1.73 m^2, either a SGLT2i or GLP1-RA with proven CV benefit is recommended principally to reduce CV risk [1, 3]. In such T2DM subjects, the choice between SGLT2i and GLP1-RA is largely determined by the coexistence of HF, particularly HF with left ventricular ejection fraction (EF) <45% [3]. It is noteworthy that the risk of HF hospitalizations or new-onset HF decreases on SGLT2i but not on GLP1-RA that have a neutral effect on HF hospitalizations, which gives priority to SGLT2i in T2DM and HF [3]. In sharp contrast, either a GLP1-RA with proven CV benefit (reducing predominantly atherosclerosis-dependent events) or a SGLT2i should be used in T2DM and established atherosclerotic CV disease (ASCVD) or other indicators of high CV risk, i.e. age >55 years and coronary, carotid or peripheral artery stenosis over 50%, or the presence of left ventricular hypertrophy) [3]. Unlike with orally administered SGLT2i, only subcutaneous formulations are available for GLP1-RA except for semaglutide, which can also affect drug choice. Curiously, SGLT2i and GLP1-RA can be combined with each other, so that in patients not meeting glycemic targets on a SGLT2i, a GLP1-RA as an add-on therapy to the SGLT2i may be considered and vice versa [3]. Nonetheless, this approach appears rather unrealistic for budgetary reasons. Among other possible drug combinations, SGLT2i and GLP1-RA can be used with other antidiabetic agents (insulin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP-4i)), except for the simultaneous treatment with GLP1-RA and DPP-4i [3].

Importantly, according to ADA experts, although metformin and lifestyle changes (weight management and physical activity) still remain a first-line strategy in T2DM, SGLT2i are preferred as either an additional antidiabetic drug in albuminuric T2DM subjects on metformin or may even be the drug of choice when metformin is contraindicated (at eGFR <30 mL/min/1.73 m^2, while at eGFR <45 mL/min/1.73 m^2 metformin should not be initiated, yet can be continued in a halved dose) or not tolerated [1]. Moreover, in both 2020 and 2021 ADA guidelines [2, 3], addition of SGLT2i to metformin is suggested independently of baseline HbA1c or individualized glycemic target. This approach has been a considerable change in comparison to the 2019 version of ADA guidelines [8], where additional antihyperglycemic agents, including

SGLT2i or GLP1-RA, were indicated only in those with HbA1c over the glycemic target despite metformin use for approximately 3 months. From the practical point of view, the current position has to be perceived in a wider perspective. Clearly, the proposed introduction of SGLT2i or GLP1-RA independently of HbA1c likely reflects a very low risk of possible hypoglycemia with these drugs. On the other hand, hypoglycemic episodes can be precipitated by the combination therapy in selected subjects, especially in patients receiving also sulfonylureas or insulin, which may require an adjustment of dosage. Moreover, according to the ACCORD trial [1], adverse effects of intensive glucose control (hypoglycemic episodes and mortality) were more frequent in T2DM patients with CKD.

The above summarized ADA standards of care [2, 3] have largely been reflected by the 2020 guidelines on the management of diabetic patients issued by the Polish Diabetes Association (PDA) [9]. In particular, early combination therapy. i.e. metformin with a SGLT2i or GLP1-RA,, is recommended in T2DM subjects with any of the following coexistent diseases: ASCVD, CKD or HF with reduced EF [9]. As in the ADA guidelines [3], in ASCVD either a SGLT2i or GLP1-RA with proven CV benefit should be used, while in HF SGLT2i are recommended. SGLT2i are also preferred in T2DM patients with depressed eGFR or elevated UACR, followed by GLP1-RA in subjects with contraindications to SGLT2i or not tolerating the latter class of drugs. Notably, the 2020 PDA guidelines mention also a high risk of hypoglycemia and obesity as an indication to SGLT2i or GLP1-RA owing to their safety profile and potential for weight loss [9]. Nevertheless, the cost of these novel antidiabetic drugs is a major issue and reimbursement constraints profoundly limit their use not only in Poland but all over the world even in much smaller subgroups of patients with T2DM [3, 9].

The 2020 PDA guidelines [9] appear closer to the previously summarized ADA recommendations [2, 3] than the 2019 European Society of Cardiology (ESC) guidelines on diabetes, pre-diabetes, and CV diseases developed in collaboration with the European Association for the Study of Diabetes (EASD) [10]. In the latter document [10], SGLT-2i (empagliflozin, canagliflozin, dapagliflozin) or GLP1-RA (liraglutide, semaglutide, dulaglutide) are preferred over metformin in drug-naïve T2DM patients with ASCVD or high/very high CV risk and the addition of metformin is suggested when HbA1c remains over target despite SGLT2i or GLP1-RA monotherapy. The definition of very high CV encompasses not only target organ damage (albuminuria, reduced eGFR, left ventricular hypertrophy or diabetic retinopathy), but also the presence of at least 3 out of 5 CV risk factors (older age, hypertension, dyslipidemia, obesity and smoking) [9]. The definition of high CV risk is especially broad, including patients with DM duration ≥10 years without target organ damage plus any other additional CV risk factor of the above set [10]. Consequently, metformin monotherapy would be restricted to a relatively low number of T2DM patients with moderate

CV risk [10]. Therefore, it is widely disputed whether the 2019 ESC/EASD recommendations can really be implemented in the clinical practice, or rather may be perceived as a contribution to future balanced optimization of risk stratification in T2DM.

Regardless of budgetary considerations, it has been argued that the majority of T2DM subjects recruited to CVOTs with SGLT-2i and GLP1-RA were receiving metformin. Obviously, a trial comparing SGLT2i or GLP1-RA with versus without metformin is unlikely to be performed in SGLT2i/GLP1-RA era. Thus, the ADA and PDA-recommended use of SGLT2i/GLP1-RA as add-on to metformin appears reasonable, with the choice of a second agent driven by the patient profile, especially the prevalence of ASCVD and HF as well as eGFR value and the magnitude of albuminuria.

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Conflict of interest

None declared.

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