COMMENTARY

What Is the Best Medicine for Chronic Kidney Disease in Diabetes?

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The dihydropyridine finerenone is a new mineralocorticoid receptor antagonist recently approved for the treatment of albuminuric chronic kidney disease (CKD) in patients with type 2 diabetes (T2D). It is well known that aldosterone, beyond its role in body fluid and electrolyte balance, is implicated in insulin resistance and the metabolic syndrome (1) and thus in T2D. As aldosterone is also a recognized mediator of oxidative stress, inflammation, and organ fibrosis, finally causing renal and cardiovascular injury (2), in CKD it makes sense to use drugs that inhibit the binding of aldosterone to its receptor. Earlier steroidal mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, had major safety concerns in terms of severe hyperkalemia, together with other undesirable side effects, e.g., gynecomastia, erectile dysfunction, dysmenorrhea, etc. In contrast to older mineralocorticoid receptor antagonists (3), finerenone has proven to be effective in reducing the action of aldosterone but with fewer side effects, including hyperkalemia. Two large phase 3 studies, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD), have shown that finerenone reduces CKD progression and cardiovascular (CV) disease in T2D patients. The FIDELIO-DKD trial studied the effects of finerenone in reducing kidney failure and kidney disease progression in patients with T2D with severely increased albuminuria and stage 3–4 CKD (4), while FIGARO-DKD studied the effect of finerenone on cardiovascular mortality and morbidity in patients with T2D and albuminuric kidney disease (5). Renal condition in patients enrolled in the FIDELIO-DKD trial (CKD end point) was worse in terms of albumin-to-creatinine ratio and average estimated glomerular filtration rate (eGFR) than that of the patients enrolled in FIGARO-DKD (CV outcome). The two trials were subsequently combined in FIDELITY, an analysis of both trials, spanning the entire spectrum of albuminuric CKD associated with T2D.

Recently, the use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) has been recommended in T2D to prevent progression of CKD (even if not albuminuric) and CV disease (6,7). Although the mechanisms of action behind the nephroprotective effects of SGLT2i are not completely understood, several trials have demonstrated renal protection in patients with diabetes and even in patients without diabetes (8). As both SGLT2i and finerenone have been proven to prevent the progression of CKD in albuminuric T2D patients, a question arises: What is the best medicine for CKD in diabetes?

Through the FIDELITY analysis, Rossing et al. (9) explore the effects of finerenone on outcomes in patients with CKD and T2D receiving or not receiving SGLT2i. They find that finerenone provides kidney and CV benefits irrespective of treatment with an SGLT2i, confirming the role of this new aldosterone receptor antagonist in improving renal and CV outcomes in albuminuric patients with diabetes. However, in this large analysis, it is unclear whether SGLT2i continue to exert their renal and CV protection once combined with finerenone. In Fig. 2 of Rossing et al. (9), the percent change in the albumin-to-creatinine ratio relative to baseline is represented in four groups (with and without SGLT2i combined with and without finerenone). While the protective action of finerenone appears evident in both groups (with and without SGLT2i), SGLT2i appear not to add any further protective effect, both in the finerenone groups (with and without SGLT2i, the two blue lines) and in the placebo groups (with and without SGLT2i, the two orange lines).

Again, the results of the Rossing et al. (9) study create a dilemma for the clinician: finerenone or SGLT2i? If there is no cumulative nephroprotection, does it make sense to continue SGLT2i once finerenone is started? Further, as SGLT2i have no glucose-lowering effect in patients with low eGFR, we might be tempted to suspend their use. The FIDELITY analysis, however, does not demonstrate that SGLT2i have no nephroprotective effects when finerenone is added. When two treatment groups are compared, lack of a statistically significant difference does not necessarily mean that the

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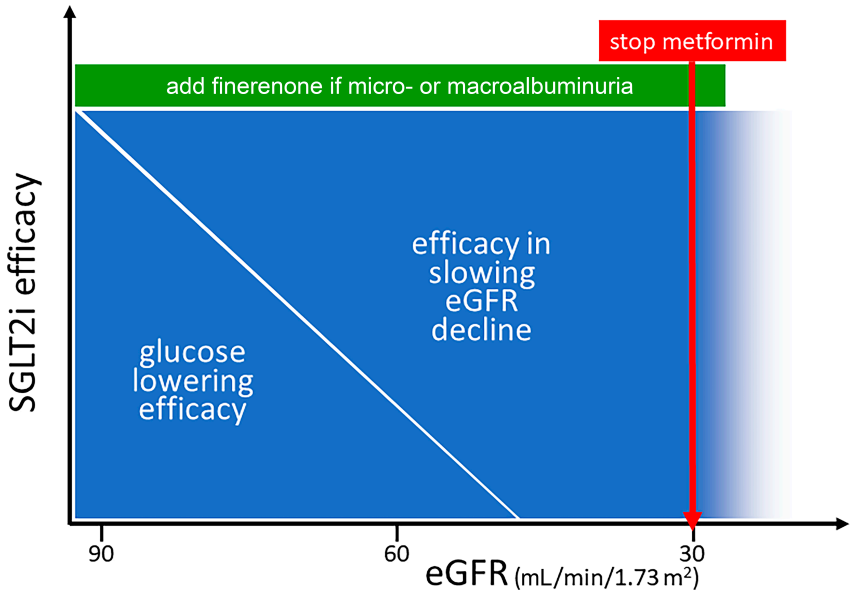

Figure 1—Efficacy of SGLT2i over the entire range of eGFR values. When eGFR is close to normal range (left), SGLT2i express their maximal efficacy as glucose-lowering agents. When eGFR declines, SGLT2i lose their glucose-lowering efficacy, but it is at this point that their action in slowing down eGFR decline becomes essential as an attempt to delay the significant clinical end point of an eGFR ≤30 mL/min/1.73 m^2, when metformin must be suspended. Whatever the eGFR, in presence of micro- or macroalbuminuria finerenone should be added. This addition will not reduce the protective effects of SGLT2i, at least for heart failure.

two treatments are similar but rather that the study could not demonstrate a difference. The most common reason for this kind of result (very frequent in subanalyses) is the lack of adequate statistical power. In the FIDELITY analysis, only 6.7% of enrolled patients were on SGLT2i at baseline, and 8.5% started SGLT2i after the beginning of the trials. When examining patients receiving or not receiving an SGLT2i at baseline (Fig. 1, upper panel, in Rossing et al. [9]), the high confidence intervals of the various end points do not allow the attainment of a statistical difference. Nevertheless, the hazard ratios of the different end points are numerically 20–40% lower in patients also treated with an SGLT2i. Although not statistically different, the data strongly suggest that, if adequately powered, the combined use of an SGLT2i and finerenone most probably would demonstrate an additive protective effect of the combination versus the use of just one of the two medicines. Further, the two trials correctly allowed the initiation of an SGLT2i during the studies. All the SGLT2i CV and renal trials published to date clearly evidenced that the protective effects need time before they manifest; thus, it is difficult to extrapolate these effects, since SGLT2i are initiated at different stages of the trials and, consequently, of the FIDELITY analysis. The reduction of hospitalization for heart failure, however, usually reaches a statistically significant difference within weeks. A recent trial (10) has shown that SGLT2i provide protection from heart failure a few days after treatment is started. In fact, the FIDELITY analysis shows that treatment with SGLT2i is effective in reducing heart failure (by 75%), whether it is started before baseline or after the beginning of the trials. Thus, even though the data do not demonstrate the efficacy of SGLT2i for all CV end points, it is evident that they prevent heart failure, and this is already sufficient reason to continue SGLT2i treatment once finerenone is initiated.

With the exception of the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) (11), the other two large trials on renal protection with SGLT2i (12,13) enrolled only patients with albuminuria, as the latter significantly increases risk of progression of renal and, importantly, CV disease. However, a reduced eGFR, even in the absence of albuminuria, is also a clinically relevant event in the treatment of diabetes. It is well known that eGFR declines faster in patients with T2D, and this phenomenon has significant clinical implications, including adapting the dose of several medicines. Moreover, metformin, the cornerstone of T2D treatment, must be withdrawn when eGFR reaches values ≤30 mL/min/1.73 m^2. At this stage, patients with T2D are usually already on polypharmacy treatment, and the withdrawal of metformin often compels the initiation of insulin treatment, with all the known consequences in these frail patients. Therefore, slowing the progressive reduction in eGFR to delay reaching values ≤30 mL/min (even in the absence of albuminuria) is a major clinical end point.

Several CV outcome trials, e.g., Canagliflozin Cardiovascular Assessment Study (CANVAS) (14), BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) (15), and Dapagliflozin Effect on Cardiovascular Events–Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) (16), have demonstrated that SGLT2i slow eGFR decline in patients with eGFR values >60, even without albuminuria. The impact of the class of SGLT2i on delaying eGFR progression was further demonstrated in patients with a wider range of baseline eGFR by the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) (12) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) (13) trials. Both trials enrolled only patients with albuminuria, but there is no reason to believe that the delay in eGFR decline due to SGLT2i is achievable only in these patients. The final evidence will probably come from the EMPA-KIDNEY trial (11), which specifically included patients with eGFR ≥20 but <45 mL/min/1.73 m^2, independently of albuminuria.

In summary, what is the best medicine for chronic kidney disease in T2D? While there is no doubt as to the importance of prescribing an SGLT2i (and, from today, finerenone) in patients with albuminuric CKD, the role of preventing eGFR decline (even in the absence of albuminuria) should not be neglected. This compels the use of SGLT2i over the entire range of eGFR values (Fig. 1 in Rossing et al. [9]). When eGFR is close to normal range, SGLT2i express their maximal efficacy as glucose-lowering agents. When eGFR declines, SGLT2i lose their glucose-lowering efficacy, but it is

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at this point that their action in slowing eGFR decline becomes essential. The best treatment for CKD in diabetes is prevention, whatever the medicine.

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