Renal outcomes of SGLT2 inhibitors and GLP1 agonists in clinical practice

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DIABETIC KIDNEY DISEASE

Renal outcomes of SGLT2 inhibitors and GLP1 agonists in clinical practice

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Clinical trials of sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists have shown beneficial effects of these agents on kidney outcomes in patients with type 2 diabetes mellitus. Two new cohort studies now demonstrate that these findings are generalizable to the broad range of patients seen in clinical practice.

Refers to Pasternak, B. et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian Cohort Study. *Br. Med. J.* **369**, m1186 (2020) | Pasternak, B. et al. Use of glucagon-like peptide 1 receptor agonists and risk of serious renal events: Scandinavian Cohort Study. *Diabetes Care* **43**, 1326–1335 (2020).

When the FDA issued a guideline in 2008 that required pharmaceutical companies to evaluate the cardiovascular safety of new glucose-lowering drugs, no one could foresee that this directive would be the prelude to a revolution in the prevention and treatment of diabetic kidney disease. Since then, the cardiovascular safety of dipeptidyl peptidase 4 (DPP4) inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists has been established in large cardiovascular outcomes trials (CVOTs). While CVOTs with DPP4 inhibitors confirmed their safety but did not show cardiovascular or renal efficacy, SGLT2 inhibitors and GLP1 receptor agonists were found not only to be safe, but also to improve cardiovascular outcomes[1,2]. Furthermore, these CVOTs showed that SGLT2 inhibitors delayed the progression of chronic kidney disease (CKD) — a finding that was confirmed in a dedicated kidney outcome trial with the SGLT2 inhibitor canagliflozin[3]. GLP1 receptor agonists also seemed to have beneficial effects on decline in estimated glomerular filtration rate (eGFR), albeit smaller than the effects of SGLT2 inhibitors. Given the accumulating evidence, clinical practice guidelines now recommend SGLT2 inhibitors and GLP1 receptor agonists for patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease.

But how do the beneficial renal effects in CVOTs with SGLT inhibitors and GLP1 receptor agonists translate into clinical practice? Participants in clinical trials are selected according to strict criteria, chosen to maximize the chance of successfully addressing the primary study objective. Most participants in CVOTs with SGLT2 inhibitors and GLP1 receptor agonists had a history of cardiovascular disease, whereas in clinical practice most patients are at risk of cardiovascular disease, but do not have an established cardiovascular condition[4] (FIG. 1). In fact, analyses that evaluated the representativeness of CVOTs with both SGLT2 inhibitors and GLP1 receptor agonists found that the vast majority of patients with T2DM in everyday practice would not be eligible to participate in these studies[5,6]. Therefore, data on the effects of SGLT2 inhibitors and GLP1 receptor agonists in clinical practice are highly welcome. Two large Scandinavian cohort studies now provide important insights into this topic[7,8].

In one cohort study, the researchers compared the occurrence of serious renal events among 29,887 new users of SGLT2 inhibitors and 29,887 matched, new users of DPP4 inhibitors[7]. DPP4 inhibitors were chosen as comparator as they are used in similar clinical situations, but have no effects on kidney outcomes. Importantly, only 19% of patients in the cohort had cardiovascular disease and 3% had CKD. The primary outcome was a composite renal event defined as kidney replacement therapy, hospital admission for renal events or death from renal causes. Over a mean follow-up of 1.7 years (SD 1.0 years), use of SGLT2 inhibitors reduced the risk of the composite renal outcome by 58% compared with DPP4 inhibitors. This effect was driven by lower rates of kidney replacement therapy and hospitalization for renal events. Although the absolute risk reduction was largest in patients with cardiovascular disease or CKD, SGLT2 inhibitor use also reduced the risk of renal events in patients with a low cardiovascular risk, a group that has been underrepresented in clinical trials.

The other cohort study used a similar design, but compared the renal effects of GLP1 receptor agonists with those of DPP4 inhibitors[8]. Again, propensity scores were used to match new users of GLP1 receptor agonists and DPP4 inhibitors ($n = 38{,}731$ in each group). The proportion of patients with cardiovascular disease or CKD was 18% and 5%, respectively. Over a mean follow-up of

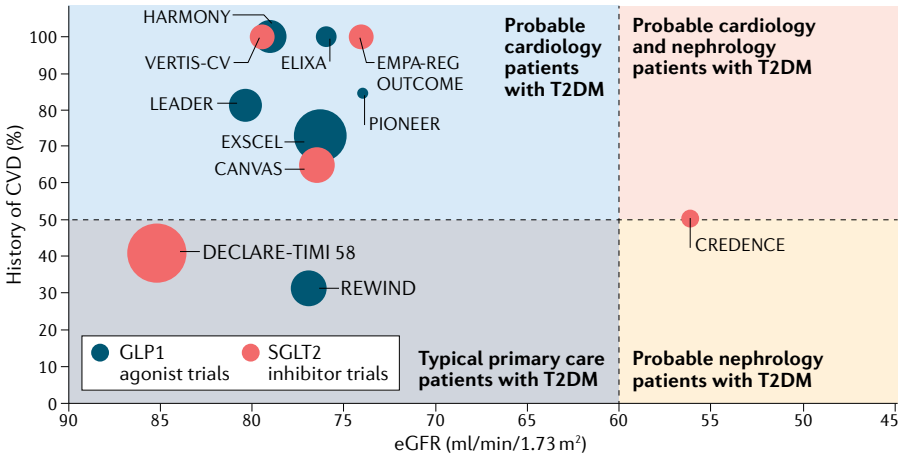

Fig. 1 | **Patient cohorts enrolled in clinical trials with SGLT2 inhibitors and GLP1 receptor agonists.** Most trials enrolled selected patient cohorts with cardiovascular disease (CVD) and preserved kidney function who would typically be seen by cardiologists. Patients seen by general practitioners or nephrologists were underrepresented in these trials, which limits the generalizability of the trial findings to clinical practice. The size of each bubble is proportional to the number of patients enrolled in each trial (for example, DECLARE-TIMI had 17,160 participants and PIONEER had 3,183). eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus. Adapted with permission from REF.[4], Wiley-VCH.

> data on the effects of SGLT2 inhibitors and GLP1 receptor agonists in clinical practice are highly welcome

3.0 years (SD 1.7 years) use of GLP1 receptor agonists, compared with DPP4 inhibitors, was associated with a 27% lower risk of the same primary composite renal outcome as used in the first study. The beneficial effects of GLP1 receptor agonists were consistent for each of the different components of the composite renal outcome and the effect of GLP1 receptor agonists was independent of the presence of cardiovascular disease. Similarly to SGLT2 inhibitors, GLP1 receptor agonists were associated with a significantly larger benefit in patients with a history of CKD than in those without CKD.

These cohort studies are important as they demonstrate that SGLT2 inhibitors and GLP1 receptor agonists slow the progression of CKD in patients with T2DM in a real-world setting. These findings are in line with those from the CVD-REAL 3 study — a multinational analysis of data from real-world clinical practice databases, which showed that initiation of SGLT2 inhibitors was associated with greater renal protection than other glucose-lowering drugs[9]. Although clinical registries can provide important information about the effectiveness of drugs in clinical practice, causal inferences are difficult to make owing to the observational design of registry studies. Well-designed randomized controlled trials are thus needed to provide definitive evidence about the renal efficacy of these agents. In this respect, it is noteworthy that the DAPA-CKD trial, which investigated the effect of the SGLT2 inhibitor dapagliflozin in participants with moderate-to-severe CKD with or without T2DM, was stopped early because of overwhelming efficacy[10]. Randomized controlled trial evidence on the effects of GLP1 receptor agonists on renal outcomes is currently lacking. The ongoing FLOW trial (NCT03819153), which is investigating the effect of semaglutide versus placebo on renal outcomes in participants with T2DM and CKD, will provide more definitive evidence.

Despite the evidence for the clinical benefits of SGLT2 inhibitors and GLP1 receptor agonists in a broad range of patients, and the incorporation of both drugs in international guidelines, several barriers remain to be overcome for their successful implementation in clinical practice. Currently, most SGLT2 inhibitors and some GLP1 receptor agonists are approved for use in patients with T2DM and eGFR >30 ml/min/1.73 m^2 or >45 ml/min/1.73 m^2, despite the fact that they may benefit patients with eGFR levels below this threshold. In addition, education of care providers and patients is needed to create awareness of the non-glycaemic benefits of SGLT2 inhibitors and GLP1 receptor agonists. Moreover, the high costs associated with both drug classes may pose a barrier to their widespread use, particularly in low-income regions. A combined effort by professional organizations and patient advocacy groups is needed to realize the uptake of these agents as standard of care for the prevention of renal and cardiovascular complications in patients with T2DM. The studies by Pasternak and colleagues emphasize the urgency of achieving this goal.

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1. Zelniker, T. A. et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* **393**, 31–39 (2019).
2. Kristensen, S. L. et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* **7**, 776–785 (2019).
3. Perkovic, V. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* **380**, 2295–2306 (2019).
4. Giorgino, F., Vora, J., Fenici, P. & Solini, A. Cardiovascular protection with sodium-glucose co-transporter-2 inhibitors in type 2 diabetes: does it apply to all patients? *Diabetes Obes. Metab.* https://doi.org/10.1111/dom.14055 (2020).
5. Birkeland, K. I. et al. How representative of a general type 2 diabetes population are patients included in cardiovascular outcome trials with SGLT2 inhibitors? A large European observational study. *Diabetes Obes. Metab.* **21**, 968–974 (2019).
6. Knudsen, J. S., Thomsen, R. W., Pottegård, A., Knop, F. K. & Sørensen, H. T. Differences between randomized clinical trial patients and real-world initiators of the glucagon-like peptide 1 receptor agonist liraglutide. *Diabetes Care* **41**, e133–e135 (2018).
7. Pasternak, B. et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. *Br. Med. J.* **369**, m1186 (2020).
8. Pasternak, B. et al. Use of glucagon-like peptide 1 receptor agonists and risk of serious renal events: Scandinavian cohort study. *Diabetes Care* **43**, 1326–1335 (2020).
9. Heerspink, H. J. L. et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol.* **8**, 27–35 (2020).
10. Heerspink, H. J. L. et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol. Dial. Transplant.* **35**, 274–282 (2020).

Competing interests

H.L.H. has served as a consultant for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, and Retrophin and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen. A.B.v.d.A-v.d.B. declares no competing interests.