GLP-1 receptor agonists and other incretin mimetics for diabetes and chronic kidney disease—a KDIGO commentary

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Kidney Disease: Improving Global Outcomes (KDIGO) published its first Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD) in 2020 and updated the guideline in 2022.[1] These guidelines outlined a comprehensive, evidence-based approach to evaluating and treating people with diabetes and CKD to improve kidney and cardiovascular outcomes. The 2020 guideline was updated after just 2 years because multiple new clinical trials with evidence directly relevant to the guideline recommendations were published quickly. The 2022 Clinical Practice Guideline featured updates on sodium-glucose cotransporter-2 inhibitors (SGLT2i), nonsteroidal mineralocorticoid antagonists, and overall comprehensive care.[1]

The rapid pace of new evidence in the management of diabetes and CKD has continued, with particularly noteworthy advances in the application of drugs that mimic incretin hormones, that is, glucagon-like peptide receptor-1 agonists (GLP-1 RA) and drugs that modulate combinations of GLP-1, glucose-dependent insulinotropic (GIP), and glucagon receptors. The Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial evaluated the kidney effects of the GLP-1 RA subcutaneous semaglutide 1 mg once weekly among 3533 participants with type 2 diabetes (T2D) and CKD, defined by albuminuria (>100 mg/g creatinine if estimated glomerular filtration rate [eGFR] 25 to <50 ml/min per 1.73 m^2 or >300 mg/g creatinine if eGFR 50–75 ml/min per 1.73 m^2).[2] In the FLOW trial, compared with placebo, semaglutide reduced the risk of a primary composite kidney outcome by 24% (Table 1). In a *post hoc* analysis of the Study of Tirzepatide (LY3298176) Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4) study of people with T2D and elevated cardiovascular risk, tirzepatide (a dual GLP-1 RA and GIP receptor agonist) reduced a similar composite kidney endpoint by 42%, compared with insulin glargine.[3]

Other new trials evaluated the effects of incretin mimetics among people without diabetes. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial evaluated the effects of subcutaneous semaglutide 2.4 mg once weekly among 17,604 people without diabetes who were living with overweight or obesity and prevalent atherosclerotic cardiovascular disease. In SELECT, compared with placebo, semaglutide reduced the risk of a primary composite cardiovascular outcome by 20% and the risk of a secondary kidney outcome by 22% (Table 1).[4,5] In the SeMaglutide and Albuminuria Reduction Trial (SMART) in obese individuals without diabetes, in people with albuminuria and overweight or obesity but not diabetes, subcutaneous semaglutide 2.4 mg per week reduced albuminuria by 52%, compared with placebo.[6]

The KDIGO 2020 and 2022 Clinical Practice Guidelines recommend using a long-acting GLP-1 RA with documented cardiovascular benefits for people with T2D and CKD who have not achieved individualized glycemic targets despite the use of metformin and SGLT2i treatment, or who are unable to use those medications.[1] The rationale for this recommendation included demonstrated cardiovascular benefits of GLP-1 RA (which were consistent across strata of albuminuria and eGFR) and possible kidney benefits observed in small trials and *post hoc* analyses of cardiovascular outcome and glucose-lowering trials (which often evaluated composite kidney outcomes that were driven by incident macroalbuminuria). The KDIGO Work Group recommended that a GLP-1 RA be added to SGLT2i and metformin preferentially to other glucose-lowering medication because of these benefits. The Work Group also noted as a practice point that it is reasonable to "make

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room" in the glycemic regimen for a GLP-1 RA by replacing dipeptidyl peptidate-4 inhibitors, discontinuing another glucose-lowering medication with fewer benefits (such as sulfonylurea), or carefully reducing the dose of insulin. Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, the GLP-1 RA recommendation was classified as Level 1 (i.e., Most people should receive the recommended course of action), with a B grade for certainty of evidence (i.e., the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different). Now, new data from these aforementioned incretin mimetic trials provide additional evidence supporting this current recommendation.

New incretin mimetic data also raise the question of whether indications for these drugs among people with T2D and CKD should be broadened beyond a need for glycemic control. Mechanisms through which incretin mimetics improve kidney and cardiovascular outcomes remain unclear. While these drugs potently reduce hemoglobin A1c, glycemic control does not appear to be the main mechanism of kidney and cardiovascular risk reduction. In FLOW, the benefits of semaglutide did not differ by baseline hemoglobin A1c.[2] In addition, cardiovascular and kidney benefits of semaglutide were apparent among participants without diabetes in the SELECT and SMART trials.[4–6]

Among people with T2D and CKD, obesity, albuminuria, and prevalent cardiovascular disease are potentially compelling indications for incretin mimetics, in addition to the need for improved glycemic control. Among people with obesity, trials of incretin mimetics have reported reduced weight by up to 24% compared with placebo.[7] Many participants in trials studying the effects of incretin mimetics were also living with obesity, and the SELECT and SMART trials only enrolled participants living with overweight or obesity.[4–6] Given the high prevalence of obesity in people with diabetes and CKD, incretin mimetic therapy offers the opportunity to improve glucose control, weight, and clinical outcomes (both kidney and cardiovascular) simultaneously.

People with T2D and albuminuria are at high absolute risk of both CKD progression and cardiovascular events, therefore these people would be expected to have the highest absolute risk reductions with incretin mimetics. To date, the FLOW trial has provided the strongest evidence in support of incretin mimetic use for kidney protection, and albuminuria was a key inclusion criterion.[2] People with T2D, CKD, and known cardiovascular disease are also at high cardiovascular risk, inclusive of heart failure and atherosclerotic cardiovascular disease. As such, these individuals may be expected to have high absolute cardiovascular risk reduction from incretin mimetics. In fact, clinical practice guidelines from the American Diabetes Association, European Association for the Study of Diabetes, American Heart Association/American College of Cardiology, and European Society of Cardiology already recommend incretin mimetics for people with T2D and cardiovascular disease, including those with CKD.

An alternative approach may be to offer all people with T2D and CKD an incretin mimetic, without regard to additional indications. Such a recommendation would parallel that for SGLT2i, which are recommended for all people with T2D and CKD (when initiated with eGFR $\geq$20 ml/min per 1.73 m^2) because of their proven large kidney and cardiovascular benefits across strata of albuminuria (including normal urinary albumin excretion), eGFR, and other key clinical characteristics. Indeed, most people with T2D and CKD are likely to have inadequately controlled blood glucose, obesity, albuminuria, cardiovascular disease, or a combination of these characteristics. This approach is potentially complicated by the potent effects of incretin mimetics on lowering glucose levels and weight, which may not be required for all people, as well as high cost in many settings.

It is worth considering whether incretin mimetics, along with SGLT2i, should supplant metformin as a first-line treatment for T2D and CKD. The American Diabetes Association and European Association for the Study of Diabetes guidance for the management of hyperglycemia in T2D has already recommended the use of GLP-1 RA or SGLT2i before metformin in people with kidney or atherosclerotic disease or heart failure.[8]

Incretin mimetics may also have a role in the treatment of people with CKD who do not have T2D. As for SGLT2i, initial studies of incretin mimetics logically focused on people with T2D, but as benefits were observed and suggested to be independent of glycemia, inclusion criteria broadened to other CKD groups. Indeed, trials have confirmed the weight and cardiovascular benefits of incretin mimetics among people

Table 1 | Selected studies examining the kidney and cardiovascular impact of glucagon-like peptide receptor-1 agonists published since the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

Study	Population	N	Intervention	Comparator	Outcome Definition	Follow-up	Effect Estimate
FLOW[2]	T2D and CKD[a]	3533	Semaglutide 1 mg once weekly	Placebo	Primary composite kidney outcome (onset of kidney failure [dialysis, kidney transplantation, or an eGFR of <15 ml/min per 1.73 m^2], ≥50% reduction in eGFR from baseline, or death from kidney-related or CV causes)	Median: 3.4 yr	HR: 0.76; 95% CI: 0.66–0.88
SELECT[4,5]	Preexisting CV disease and a BMI of ≥27 kg/m^2 but no history of diabetes	17,604	Semaglutide 2.4 mg once weekly	Placebo	Primary composite CV outcome (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis)	Mean: 39.8 mo	HR: 0.80; 95% CI: 0.72–0.90
					Secondary composite kidney outcomes (death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent eGFR <15 ml/min per 1.73 m^2, persistent ≥50% reduction in eGFR or onset of persistent macroalbuminuria)	Median: 41.9 mo	HR: 0.78; 95% CI: 0.63–0.96
SMART[6]	CKD[b] and BMI ≥27 kg/m^2	101	Semaglutide 2.4 mg once weekly	Placebo	Primary endpoint was percentage change from baseline in UACR at week 24	24 wk (5.5 mo)	−52.1%; 95% CI: −65.5% to −33.4%
SURPASS-4[3] (*post hoc* analysis)	T2D and elevated CV risk	2002	Tirzepatide (5 mg, 10 mg, or 15 mg once weekly)	Insulin glargine	Composite kidney outcome was a composite of time to first occurrence of eGFR decline of ≥40% from baseline, end-stage kidney disease, death owing to kidney failure, or new-onset macroalbuminuria	Median: 104 wk (23.9 mo)	HR: 0.58; 95% CI: 0.43–0.80

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.
[a]CKD was defined by albuminuria (>100 mg/g creatinine if eGFR 25 to <50 ml/min per 1.73 m^2 or >300 mg/g creatinine if eGFR 50–75 ml/min per 1.73 m^2).
[b]CKD defined as eGFR ≥25 ml/min per 1.73 m^2 and UACR ≥30 and <3,500 mg/g.

without diabetes.[4–7] Additional trials among people with CKD who do not have T2D would be useful.

People with type 1 diabetes (T1D) also have a high need for new kidney- and cardiovascular-protective therapies. Most published trials of new drugs for diabetes and CKD (including incretin mimetics, SGLT2i, and nonsteroidal mineralocorticoid antagonists) have excluded people with T1D. Recommendations for use of these new drugs do not apply to people with T1D, leaving clinicians with few treatment options. Although GLP-1 RA improve glycemic control and reduce weight in T1D, their effects on kidney and cardiovascular disease remain unknown.[9]

KDIGO plans to address the questions discussed in this commentary in an upcoming updated clinical practice guideline. In the meantime, the strong recommendation to use long-acting GLP-1 RA with documented cardiovascular benefits for people with T2D and CKD who have not achieved individualized glycemic targets despite the use of SGLT2i, with or without metformin, or who are unable to use those medications, remains appropriate. This recommendation has been strengthened by randomized clinical trials published since 2022. Implementation of proven therapies consistently lags behind evidence and guidelines, and greater efforts are needed to implement this recommendation as well as other strong recommendations in the KDIGO Diabetes Management in CKD and KDIGO Evaluation and Management of CKD guidelines.[1] Broader use of incretin mimetics, beyond the indication specifically recommended in the KDIGO guidelines, may be considered on a case-by-case basis taking into consideration new data, regulatory approvals, cost, and, as always, individual patient characteristics and preferences.

DISCLOSURE

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