Clinical Therapeutics xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Original Research

# No Differences in Kidney Function Decline Between People With Type 2 Diabetes Starting a Sodium-Glucose Cotransporter 2 Inhibitor or a Glucagon-like Peptide-1 Receptor Agonist: A Real-world Retrospective Comparative Observational Study

Sara Bodini, MD[#], Silvia Pieralice, MD[#], Luca D'Onofrio, MD, PhD, Carmen Mignogna, MD, Lucia Coraggio, MD, Rocco Amendolara, MSc, Renata Risi, MD, Mauro Salducci, MD, Raffaella Buzzetti, MD, PhD[*], Ernesto Maddaloni, MD, PhD

*Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy*

ARTICLE INFO

*Key words:*
Chronic kidney disease
Diabetes mellitus
Diabetic nephropathy
GLP1RA
Glucagon-like peptide-1 receptor agonist
Nephroprotective action
SGLT2i
Sodium-glucose cotransporter 2 inhibitor

ABSTRACT

*Purpose:* Diabetic nephropathy represents the leading cause of end-stage kidney disease in developed countries. Cardiovascular outcome trials have found that in participants who received a glucagon-like peptide-1 receptor agonist (GLP1RA) and a sodium-glucose cotransporter 2 inhibitor (SGLT2i), the risk of incidence and progression of diabetic nephropathy in type 2 diabetes mellitus was reduced. The aim of this study was to compare the decline in estimated glomerular filtration rate (eGFR) among people taking a GLP1RA with that among people taking an SGLT2i in a real-world setting.

*Methods:* Data for 478 patients with type 2 diabetes mellitus who initiated therapy with a GLP1RA (n = 254) or an SGLT2i (n = 224) between January 1, 2018 and December 31, 2021 were extracted. The primary outcome was any reduction ≥30% in eGFR after the start of therapy. Weight loss and drug discontinuation were also assessed.

*Findings:* Over a median follow-up of 24 months, an eGFR reduction ≥30% occurred in 34 of 254 patients (13.4%) starting a GLP1RA and in 26 of 223 patients (11.6%) starting an SGLT2i (hazard ratio = 0.89; 95% CI, 0.54–1.49; $P = 0.67$). Median eGFR change over the whole follow-up was similar between groups (SGLT2i: median, –2 mL/min/1.73 m$^2$; 25th, 75th percentile, –13, 8 mL/min/1.73 m$^2$; GLP1RA: median, 0 mL/min/1.73 m$^2$; 25th, 75th percentile, –10, 7 mL/min/1.73 m$^2$; $P = 0.54$). No worsening of kidney function was observed, even when considering the ratio eGFR mean. The value of eGFR at baseline indicated a statistically significant indirect correlation with the observed absolute value of eGFR change over the follow-up ($\rho = -0.36$; $P < 0.001$). The difference in eGFR changes over time observed by eGFR categories was statistically significant ($P = 0.0001$) in both treatment groups. No significant differences in weight loss and drug discontinuations were observed between groups.

*Implications:* Although acting on different molecular mechanisms, both GLP1RA and SGLT2i might have similar effects on eGFR decline in diabetes, as suggested by the results of the present study conducted in a real-world setting. (*Clin Ther*. 2024;46:XXX–XXX) © 2024 Elsevier HS Journals, Inc.

## Introduction

Diabetic nephropathy (DN) is the main cause of end-stage kidney disease in developed countries. It is a microvascular complication of diabetes and affects approximately 40% of patients with type 2 diabetes mellitus (T2DM) and 30% of those with type 1 DM worldwide.[1] Clinically, this condition presents with persistent albuminuria and a progressive decline in glomerular filtration rate, leading to chronic kidney disease (CKD). DN is diagnosed when persistent albuminuria occurs on 2 or more occasions of early morning urine samples, separated by at least 3 months. Risk of developing DN is directly proportional to diabetes duration. In addition, poor glycemic control and hypertension status are major risk factors for its development. Clinical practice guidelines[2] recommended a multitarget approach to reduce the risk of CKD

[*] Address correspondence to: Raffaella Buzzetti, MD, PhD, Department of Experimental Medicine, Sapienza University of Rome, Viale Regina Elena 324, 00161, Rome, Italy.
*E-mail address:* raffaella.buzzetti@uniroma1.it (R. Buzzetti).
[#] These authors contributed equally to this work.

https://doi.org/10.1016/j.clinthera.2024.04.009
Accepted 15 April 2024
Available online xxx


Please cite this article as: S. Bodini, S. Pieralice, L. D'Onofrio et al., No Differences in Kidney Function Decline Between People With Type 2 Diabetes Starting a Sodium-Glucose Cotransporter 2 Inhibitor or a Glucagon-like Peptide-1 Receptor Agonist: A Real-world Retrospective Comparative Observational Study, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2024.04.009

or its progression in people with diabetes. This includes weight, blood pressure, and lipid and blood glucose control with both lifestyle and pharmacologic interventions. Inhibition of the renin-angiotensin system through angiotensin converting enzyme inhibitors and angiotensin receptor blockers is strongly recommended in patients with incipient or overt DN. Furthermore, results of cardiovascular outcome trials[3–11] have suggested renal benefits associated with both sodium-glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP1RA). Renal benefits of SGLT2i were then confirmed in randomized controlled trials (RCTs)[12,13] specifically designed to assess the long-term efficacy and tolerability of this drug class in patients with CKD, leading to the most recent recommendation preferring SGLT2i for treating patients with T2DM and signs of kidney damage. However, to date, the FLOW study[14] is the only terminated renal outcome trial testing a GLP1RA, semaglutide, on progression of renal impairment and on the risk of renal and cardiovascular mortality in patients with T2DM and CKD. The trial was discontinued early after an interim analysis indicated clear efficacy on a renal composite outcome. Although no RCT has been conducted to compare kidney outcomes in patients treated with SGLT2i and GLP1RA, 2 observational studies,[14,15] both carried out in Asian people, performed a head-to-head comparison of these agents.

In the lack of data from head-to-head comparison RCTs, health care data can shed light on the comparative effectiveness of these agents to guide decision making. In the present study, we aimed to investigate the comparative effectiveness of SGLT2i and GLP1RA on eGFR decline in routine clinical practice.

## Methods

### *Study Design and Population*

We conducted a retrospective observational study in adults with T2DM who attended the Diabetes Unit of Umberto I General Hospital, Sapienza University of Rome, Italy, and who initiated therapy with a GLP1RA or an SGLT2i between January 1, 2018 and December 31, 2021. Data from patients meeting the following inclusion criteria were included in the analysis: (1) established diagnosis of T2DM; (2) 18 years or older; and (3) available data about the kidney outcome collected at least 6 months after the start of treatment. The date of initiation of therapy with GLP1RA or SGLT2i was defined as the cohort entry date and start of follow-up (baseline, T0). Exclusion criteria were (1) treatment with GLP1RA in preconstituted combination with insulin; (2) simultaneous therapy with both GLP1RA and SGLT2i; and (3) history of dialysis or kidney transplantation. An overview of the study design is presented in Figure 1.

### *Data Collection*

The following clinical and biochemical data were extracted from the electronic medical records of our hospital in April 2023: age, gender, disease duration, height, weight, body mass index (BMI; calculated as kg / $m^2$), presence of diabetic retinopathy, history of diabetic neuropathy, previous major cardiovascular event (defined as myocardial infarction, coronary revascularization, peripheral artery revascularization, or ischemic stroke), diabetes medications, antihypertensive therapy, fasting blood glucose level, glycosylated hemoglobin (HbA1c), serum creatinine, and urine albumin. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation without correction for race using routine plasma creatinine measurements. All covariates were extracted at baseline. Data for BMI, fasting blood glucose, HbA1c, serum creatinine, eGFR, urine albumin, and use of GLP1RA and SGLT2i were extracted at 6 and 12 months after baseline and then yearly for up to 36 months, or until the last visit of the patient at the study center. For patients who discontinued treatment with GLP1RA or SGLT2i, the reason for the interruption was also extracted.

### *Definitions of Outcomes*

The primary outcome of this study was any reduction ≥30% in eGFR after the start of the therapy.

Secondary outcomes were weight loss, defined as a ≥5% reduction in BMI, and drug discontinuation, defined as an interruption of the study drug without subsequent reassumption.

### *Statistical Analyses*

Descriptive statistics are presented for categorical variables as numbers and percentages, and for continuous variables as appropriate measures of central tendency and dispersion. The distribution of variables was tested graphically and with the Shapiro-Wilk normality test. Groups were compared using Student *t* test, Kruskal-Wallis, $\chi^2$, or Fisher exact tests, as appropriate. Incidence rates for primary and secondary outcomes were calculated per 1000 person-months in the 2 study groups. Time-to-event analyses comparing participants starting a GLP1RA or an SGLT2i were performed for primary and secondary outcomes using Cox proportional hazards models, and hazard ratios (HRs) with 95% CIs were calculated and reported. The proportional hazard assumption was found not to be violated when tested graphically. Age, baseline eGFR, and baseline diabetes therapy were tested in multivariate Cox proportional hazards models, together with the main exposure (treatment group) and retained in the final multivariate model if associated with the outcome at a nominal $P$ value < 0.1. The $P$ value for the association between treatment groups and the outcome in the final multivariate model are reported as $P_{adj}$ values. All analyses were conducted with an intention-to-treat approach, with patients included in the study according to their initial exposure group, regardless of subsequent changes in the exposure group.

Mean changes in eGFR, BMI, and HbA1c during the follow-up were calculated for each patient as the mean of the differences between measurements at each time point and baseline data.

Two-sided tests at the 0.05 level of significance were used for all statistical comparisons, with Stata/IC software, version 12.1 (StataCorp) and Prism software, version 10.0d (GraphPad Software) used for data analysis and graphical representations.

### *Ethics*

The study was performed in accordance with the Declaration of Helsinki, and the study procedures were approved by the local ethics committee (ref 5807/2020). The local ethics committee approved this retrospective observational study as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent, ensuring that the new privacy policy was followed.

## Results

### *Baseline Population Features*

A total of 478 patients with T2DM met all of the eligibility criteria and were included in the analysis. Among them, 224 initiated an SGLT2i and 254 initiated a GLP1RA. Baseline population features are reported in Table 1.

Compared with the SGLT2i group, patients treated with GLP1RA had an older median [25$^{th}$; 75$^{th}$ percentile] age (63 [56; 72] vs. 61 [54; 67] years; $P$ = 0.0016) and lower fasting blood glucose (153 mg/dl [129; 196] vs 166 mg/dl [135; 208], $P$ = 0.035), but similar HbA1c (7.9% [7.2; 8.3] vs 8.1% [7.2; 9.4], $P$ = 0.11). Furthermore, patients starting an SGLT2i had higher eGFR (median, 88 mL/min/1.73 $m^2$; [74; 111] vs 82 [65; 103], $P$ = 0.012), and were treated more frequently with intensive insulin therapy (multiple [3 or more] daily insulin injections or continuous subcutaneous insulin infusion). Baseline urine albumin

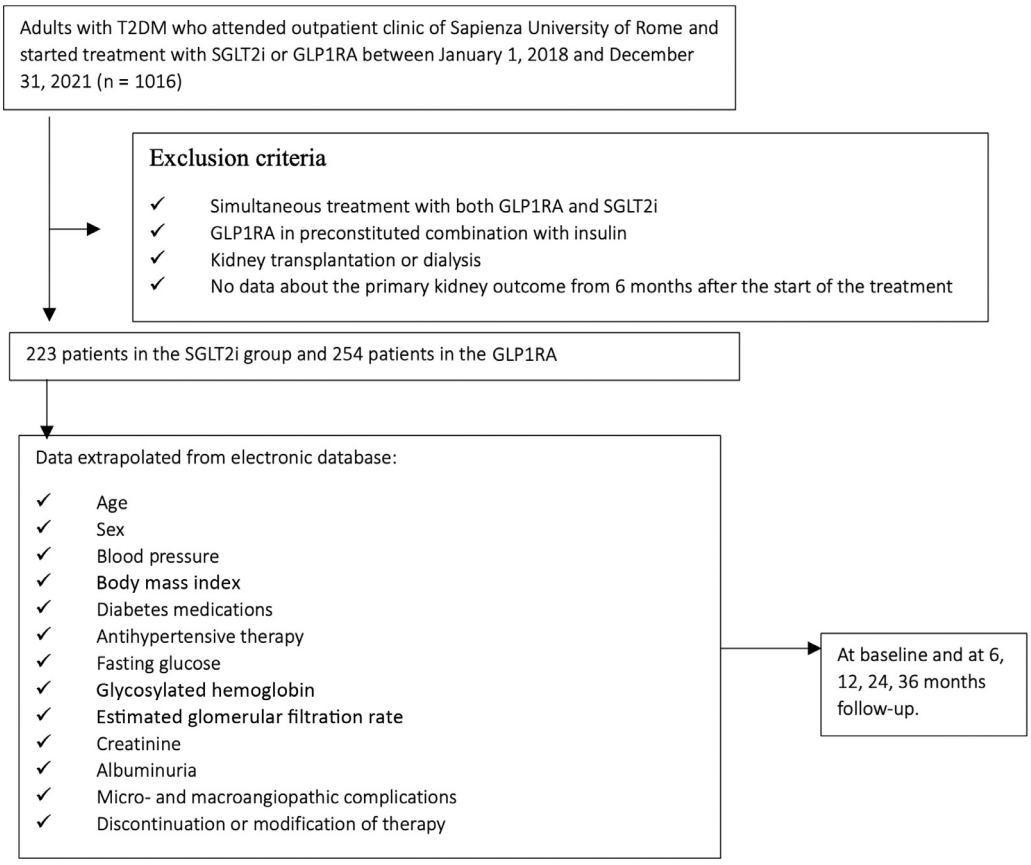


**Figure 1.** Flow diagram summarizing the study design. GLP1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus.

**Table 1**
Baseline characteristics by treatment group.

| Characteristic | Treatment | | *P* Value |
|---|---|---|---|
| | GLP1RA (n = 254) | SGLT2i (n = 224) | |
| Observations, n | 254 | 224 | — |
| Gender, n (%) | | | 0.47 |
| Male | 162 (63.8) | 150 (67.0) | |
| Female | 92 (36.2) | 74 (33.0) | |
| Age, y | 63 [56; 72] | 61 [54; 67] | 0.0016 |
| Disease duration, y | 6 [2; 12] | 6 [1; 14] | 0.82 |
| BMI, Kg/m$^2$ | 30.5 [27.4; 34.3] | 31.2 [28; 34.9] | 0.43 |
| Glycemia, mg/dL | 153 [129; 196] | 166 [135; 208] | 0.035 |
| HbA1c, % | 7.9 [7.2; 8.3] | 8.1 [7.2; 9.4] | 0.11 |
| eGFR, mL/min/1.73 m$^2$ | 82 [65; 103] | 88 [74; 111] | 0.012 |
| Creatinine, mg/dL | 0.9 [65; 103] | 0.8 [0.7; 1.0] | 0.074 |
| Retinopathy, n (%) | 44 (17) | 46 (21) | 0.37 |
| Neuropathy, n (%) | 23 (9) | 27 (12) | 0.29 |
| Previous antidiabetes therapy, n (%)* | | | <0.001 |
| Diet only | 17 (6.7) | 20 (8.9) | |
| Euglycemic drugs only | 132 (52.0) | 88 (39.3) | |
| Secretagogues ± euglycemic drug | 28 (11.0) | 15 (6.7) | |
| Basal insulin ± other antidiabetes therapies | 55 (21.7) | 42 (18.8) | |
| MDI or CSII | 22 (8.7) | 59 (26.3) | |
| MACE, n (%) | 68 (27) | 49 (22) | 0.21 |
| ARB, n (%) | 75 (30) | 71 (32) | 0.61 |
| ACEi, n (%) | 96 (38) | 71 (32) | 0.16 |

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CSII = continuous subcutaneous insulin infusion; eGFR = estimated glomerular filtration rate; GLP1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycosylated hemoglobin; [25th; 75th percentile]; MACE = major adverse cardiovascular event; MDI = multiple (3 or more) daily insulin injections; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

* Euglycemic drugs: metformin, dipeptidyl peptidase 4, SGLT2i, and GLP1RA; secretagogues: sulfonylureas and glinides.

**Table 2**
Incidence rates and hazard ratios for the primary and secondary outcomes.

| Variable | GLP1RA | | | SGLT2i | | | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| | Events (n) | Incidence Rate* (95% CI) | Follow-up† | Events (n) | Incidence Rate* (95% CI) | Follow-up† | | |
| Outcome | | | | | | | | |
| Kidney‡ | 34 | 6.3 (4.5–8.8) | 5406 | 26 | 5.7 (3.9–8.3) | 4578 | 0.89 (0.54–1.49) | 0.67 |
| Weight loss§ | 102 | 27.2 (22.4–33.0) | 3756 | 103 | 36.0 (29.7–43.7) | 2862 | 1.25 (0.95–1.65) | 0.11 |
| Drug discontinuation‖ | 62 | 12.2 (9.5–15.7) | 5076 | 59 | 13.1 (9.5–15.7) | 4488 | 1.08 (0.76–1.54) | 0.68 |

GLP1RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; SGLT2i = sodium-glucose cotransporter 2 inhibitor.
* Incidence rates are per 1000 person-months.
† Follow-up is expressed as person-months.
‡ Kidney outcome was defined as any reduction in estimated glomerular filtration rate >30%.
§ Weight loss outcome was defined as a reduction in body mass index >5%.
‖ Drug discontinuation was defined as the interruption of the study drug without subsequent reassumption.

**Table 3**
Mean reduction in body mass index, glycosylated hemoglobin, and estimated glomerular filtration rate over the whole follow-up by study groups. Data are given as median (interquartile range) unless otherwise specified.

| Variable | GLP1RA | SGLT2i | *P* Value |
|---|---|---|---|
| Body mass index | –1.1 (–0.5 to –2.1) | –1.25 (–0.3 to –2.1) | 0.33 |
| Glycosylated hemoglobin, % | –1.0 (–0.20 to –1.9) | –0.9 (–0.02 to –1.9) | 0.39 |
| eGFR, mL/min/1.73 $m^2$ | 0 (–10 to 7) | –2 (–13 to –8) | 0.54 |
| Ratio eGFR mean | 1 (0.9 to 1.1) | 1 (0.9 to 1.1) | 0.46 |

eGFR = estimated glomerular filtration rate; GLP1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

data were available for only 113 people starting a GLP1RA and 65 people starting an SGLT2i. Among these, urine albumin values ≥30 mg/dL were found in 23 patients (20.4%) starting a GLP1RA and in 18 patients (27.7%) starting an SGLT2i ($P = 0.26$)

No significant differences in terms of BMI were found between study groups (median, 31.2 km/$m^2$ [28.0; 34.9] vs 30.5 kg/$m^2$ [27.4; 34.3]).

Retinopathy was present in 17% of patients treated with GLP1RA and in 21% of the SGLT2i group, and neuropathy was reported in 9% and 12% of patients, respectively. Major cardiovascular events were reported in 27% of the GLP1RA group and in 22% of the SGLT2i group. With respect to antihypertensive therapies, most patients were using an antihypertensive drug with nephroprotective action (angiotensin converting enzyme inhibitors or angiotensin receptor blockers)—68% in the GLP1RA group and 64% in the SGLT2i group.

Most patients in the GLP1RA arm were treated with dulaglutide (57.9%), followed by liraglutide (16.7%) and semaglutide (16.3%), whereas exenatide and lixisenatide were prescribed in 7.3% and 0.3% of patients, respectively. In the SGLT2i group, the most widely received drug was dapagliflozin (58.2%), followed by empagliflozin (32%) and canagliflozin (8.8%).

Median follow-up was 24 months [12; 36] in both study groups.

*Primary Outcome*

The primary outcome of any reduction >30% in eGFR occurred in 34 of 254 patients (13.4%) starting a GLP1RA, and in 26 of 223 patients (11.6%) starting an SGLT2i (HR = 0.89; 95% CI, 0.54–1.49; $P = 0.67$) (Table 2 and Figure 2A). Results did not change after adjusting for age, baseline eGFR, and baseline antidiabetes therapy ($P_{adj} = 0.53$).

Median eGFR change over the whole follow-up was similar between study groups (–2 ml/min/1.73 $m^2$ [–13; 8]; GLP1RA: 0 ml/min/1.73 $m^2$ [–10; 7], $P = 0.54$) (Table 3). No worsening of kidney function was observed, even when considering the ratio eGFR mean, calculated as the ratio of the population mean eGFR to the mean baseline eGFR.

Changes in eGFR over time had no statistically significant correlation with the main parameters assessed at baseline, that is, age ($P = 0.69$) and fasting blood glucose values ($P = 0.15$). eGFR value at baseline had a statistically significant indirect correlation with the observed absolute value of eGFR change over the follow-up ($\rho = –0.36$; $P < 0.001$). Specifically, Table 4 reports changes in eGFR according to categories of baseline kidney function (eGFR). Patients treated with GLP1RA with preserved kidney function (group 1: eGFR ≥90 mL/min/1.73 $min^2$) had a mean reduction in eGFR of –7.5 mL/min/1.73 $m^2$ (–20 to +2 mL/min/1.73 $m^2$) over time, and patients with reduced eGFR at baseline (group 2: eGFR 60–90 mL/min/1.73 $m^2$ and group 3: eGFR <30 mL/min/1.73 $m^2$) had positive changes in kidney function, with a mean increase of +1.5 mL/min/1.73 $m^2$ (–6.3 to 8.3 mL/min/1.73 $m^2$) and +4 mL/min/1.73 $m^2$ (–3.8 to 10 mL/min/1.73 $m^2$), respectively. Results among patients treated with SGLT2i were consistent with those in GLP1RA groups (Table IV), that is, a mean reduction in eGFR of –7.3 mL/min/1.73 $m^2$ (–20 to 3 mL/min/1.73 $m^2$) over time in group 1, and an improvement in eGFR level in group 2 (+1.7 mL/min/1.73 $m^2$; –7 to 10.5 mL/min/1.73 $m^2$) and group 3 (+0.38 mL/min/1.73 $m^2$; –3.5 to 9 mL/min/1.73 $m^2$). However, there were few patients in group 3 (8%).

The differences in eGFR changes over time observed by eGFR categories was statistically significant ($P = 0.0001$) in both treatment groups.

*Secondary Outcomes*

Weight loss over time was evaluable in 225 patients treated with GLP1RA and in 191 patients treated with SGLT2i (29 patients on GLP1RA and 33 patients on SGLT2i did not have BMI data collected at follow-up). Patients on GLP1RA experienced a median change in BMI of –1.1 kg/$m^2$ [–0.35; –2.1], which was similar to median BMI change observed among participants on SGLT2i (–1.25; kg/$m^2$ [–0.3; –2.1]; *P* value for the difference between groups = 0.33).

One hundred and two patients treated with GLP1RA (45%) and 103 treated with SGLT2i (54%) lost ≥5% of their baseline BMI; there were no significant differences between groups (HR = 1.25; 95% CI, 0.95–1.65; $P = 0.11$) (Table 2 and Figure 2B) or in the final multivariate model ($P_{adj} = 0.11$).

Drug discontinuation was reported in 56 patients treated with GLP1RA (22%) and 54 patients treated with SGLT2i (24.2%), with no significant differences between groups (HR = 1.08; 95% CI, 0.76–1.54; $P = 0.68$) (Table 2 and Figure 2C), also in the final multivariate model ($P_{adj} = 0.40$).

**Table 4**
Changes in estimated glomerular filtration rate by drug in different estimated glomerular filtration rate categories.

| Variable | GLP1RA | | SGLT2i | |
|---|---|---|---|---|
| | Observations, n (%) | ΔeGFR* | Observations, n (%) | ΔeGFR* |
| eGFR ≥90 mL/min/1.73 min$^2$ | 104 (40.9) | –7.5 (–20.0 to +2.0) | 109 (48.7) | –7.3 (–20.0 to +3.0) |
| eGFR 60–90 mL/min/1.73 min$^2$ | 101 (39.7) | +1.5 (–6.3 to +8.3) | 97 (43.3) | +1.7 (–7.0 to +10.5) |
| eGFR <60 mL/min/1.73 min$^2$ | 49 (19.3) | +4 (–3.8 to +10) | 18 (8) | +0.38 (–3.5 to +9) |

eGFR = estimated glomerular filtration rate; ΔeGFR = mean changes in eGFR rate over the whole follow-up compared with baseline; GLP1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor.
* *P* value for difference among eGFR categories within each group = 0.0001.

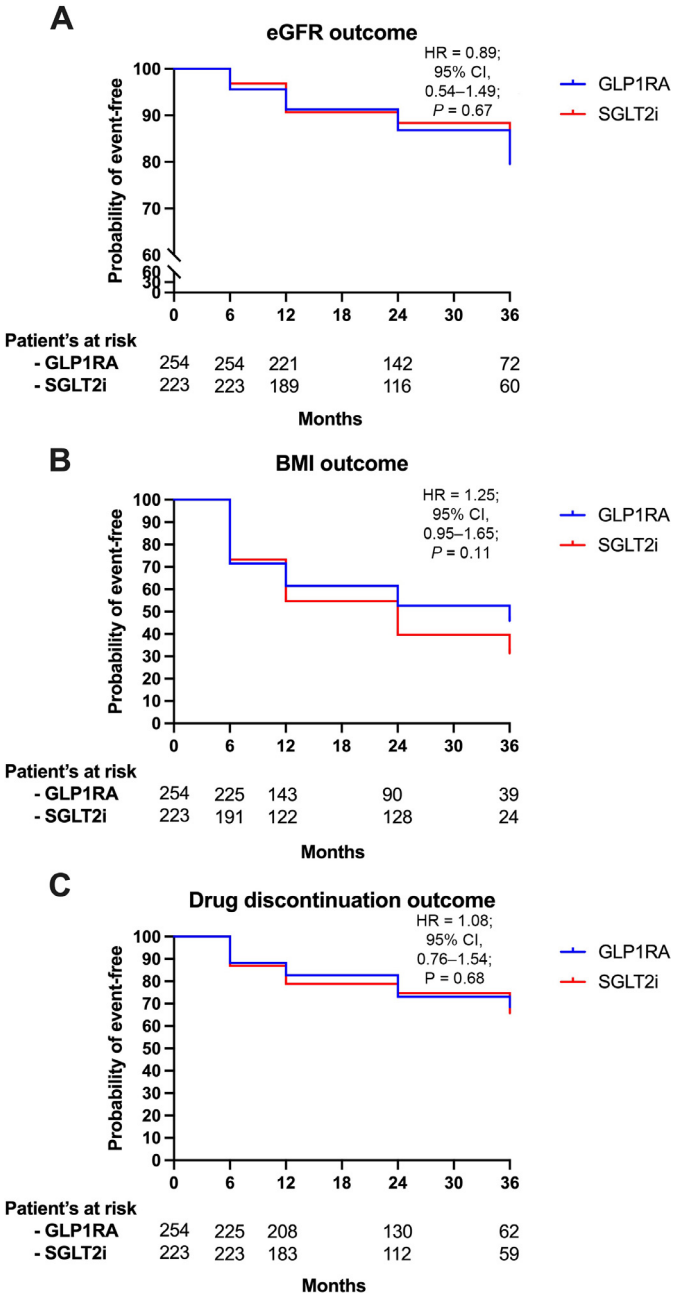


**Figure 2.** Kaplan-Meier survival function curves for the (A) primary renal outcome (estimated glomerular filtration rate) and the secondary (B) weight loss (BMI) and (C) drug discontinuation outcomes. BMI = body mass index.

Among those receiving GLP1RA, the main reasons for drug discontinuation were gastrointestinal intolerance (28.5%), glycometabolic decompensation (12.5%), excessive weight loss (7.1%), and excessive eGFR reduction (7.1%). Fewer patients discontinued therapy because of elevation of pancreatic indices (ie, amylase and lipase) (5.4%) or because of hospitalization (5.4%). Urinary infection was the most frequent reason for drug discontinuation among those receiving SGLT2i (40.7%), and worsening of glycemic control and gastrointestinal intolerance accounted for 18.5% and 5.5% of drug discontinuation reasons, respectively. Table 5 reports all causes of drug discontinuation in both groups.

## Discussion

In this observational retrospective, single-center study, 13.4% and 11.6% of patients receiving GLP1RA and on SGLT2i therapy experienced a 30% reduction in eGFR, respectively, without significant differences between the 2 drug classes over a median follow-up of 24 months. Similarly, no significant differences in BMI reduction and overall drug tolerability were observed.

The renoprotective effects of SGLT2i were initially reported in cardiovascular outcome trials,[4–7] and subsequently confirmed by the results of RCTs designed specifically to evaluate the effects of these molecules on kidney outcomes in different populations,[12,13,16] and the results of large meta-analyses[17,18] showing slower eGFR decline, lower albuminuria progression, and improvement in adverse renal end points.

The nephroprotective role of SGLT2i has been hypothesized to be linked to the restoring of the tubule-glomerular feedback and failure of glucose to enter the tubular cell. In fact, although DN has traditionally been described histologically on the basis of lesions primarily affecting the glomerulus, several studies have confirmed that the basis of the condition lies primarily in tubular cell damage, which is responsible for the development of tubular and tubule-interstitial fibrosis.[19]

Different from SGLT2i, the potential renal benefits of GLP1RA have only been suggested by secondary analyses of cardiovascular outcome trials[8–11] and by some meta-analyses,[20–22] and definitive results from ad hoc RCTs are lacking. To date, the FLOW trial[23] is the only RCT that has directly investigated the renal effects of GLP1RA, comparing injectable semaglutide 1.0 mg with placebo as an adjunct to standard of care on kidney outcomes in people with T2DM and CKD. This trial was discontinued recently on the basis of a recommendation from the independent data monitoring committee indicating that results obtained so far "met certain pre-specified criteria for stopping the trial early for efficacy."[24]

Several mechanisms of action have been hypothesized as responsible for the potential renal benefits of GLP1RA.[25] In the kidney, GLP1R is especially localized on vascular cells, and it is poorly represented on tubular cells.[26] The main signaling pathway activated by GLP1R is based on the pKA protein (cAMP-dependent protein kinase).[27] This protein inhibits the enzyme nicotinamide adenine dinucleotide phosphate oxidase, or NOX (specifically the NOX4 isoform), resulting in a decreased production of oxygen-free radicals (reactive oxygen species)[28] and, in turn, a reduction in inflammation and renal fibrosis.[29] GLP1RAs also

**Table 5**
Causes of drug discontinuation. Data are given as numbers unless otherwise specified.

| Cause | GLP1RA | SGLT2i |
|---|---|---|
| Gastrointestinal intolerance | 16 | 3 |
| Glycometabolic decompensation | 7 | 10 |
| Glycometabolic compensation | 1 | 3 |
| Urinary infections | — | 22 |
| eGFR reduction below the prescription cutoff | 4 | — |
| Excessive weight loss | 4 | — |
| Amylase and lipase elevation | 3 | — |
| Recovery | 3 | 2 |
| Patient's self-choice without any specific reported reason | 14 | 10 |
| Others (eg, tachycardia, breathlessness, and pregnancy) | 5 | 4 |

eGFR = estimated glomerular filtration rate; GLP1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

reduced expression of tumor necrosis factor-$\alpha$, monocyte chemoattractant protein 1, collagen I, $\alpha$-smooth muscle actin, and fibronectin,[30] which are all involved in the pathogenesis of DN. Several studies have also reported on the role of c-peptide in reducing tubulo-interstitial fibrosis. This could be another mechanism by which GLP1RAs protect the kidneys, as c-peptide levels were increased in patients receiving GLP1RAs.[31]

Before our study, only 2 head-to-head studies comparing SGLT2i and GLP1RA on kidney benefits had been published and both of them were carried out in Asian cohorts.[14,15] The study by Kobayashi et al[14] enrolled 806 Japanese patients with T2DM, including 541 treated with SGLT2i and 265 treated with GLP1RA, and evaluated a composite renal outcome, defined as progression of albumin to creatinine ratio status and/or deterioration of >15% in eGFR per year. According to the survey's results, SGLT2i was superior to GLP1RA in terms of the renal composite outcomes. The study was, however, limited by the presence of key differences in clinical features between participants in the 2 groups. In particular, all SGLT2i-treated patients had a previous diagnosis of CKD, whereas those receiving GLP1RA also included patients without CKD. In addition, the 2 databases (SGLT2i and GLP1RA survey) were obtained during different time periods.

To the best of our knowledge, the study by Lui et al[15] is the largest propensity score matched, cohort-based, real-world, renal study comparing head-to-head 2551 patients treated with SGLT2i and 2551 patients treated with GLP1RA. The authors reported a reduced risk of a composite renal outcome of sustained decline ≥50% of eGFR, incident macroalbuminuria, kidney-related mortality, and kidney-related dialysis or transplantation requirements among those receiving SGLT2i compared with GLP1RA. However, it should be noted that this result might have been affected, in part, by the higher proportion of patients who reached end-stage kidney disease without or before a sustained decline in eGFR ≥50% among those receiving GLP1RA than among those receiving SGLT2i. Keeping in mind the period in which the study was conducted, it should be mentioned that until 2020, the guidelines recommended the use of GLP1RA in patients with an eGFR of up to 15 mL/min/1.73 $m^2$ and an SGLT2i could only be started with an eGFR >60 mL/min/1.73 $m^2$. In fact, and similar to our results, there was no significant difference between GLP1RA and SGLT2i in the risk of sustained decline of eGFR ≥50%. In our study, we were also able to obtain data from some people starting an SGLT2i with an eGFR <60 mL/min/1.73 $m^2$, even though such group was more represented among those receiving GLP1RA in our cohort too. Although this difference between groups might have partially underestimated the renal benefits of SGLT2i compared with GLP1RA, we previously found that the higher renal benefits associated with SGLT2i were observed among people with higher eGFR.[18]

Our study also confirmed the benefits of SGLT2i and GLP1RA in terms of weight loss, as already reported in RCTs and in real-world studies.[32,33] Finally, we found in a real-world setting that the occurrence of drug discontinuation was similar among patients receiving GLP1RA and patients receiving SGLT2i, and confirmed the tolerability profile of both drug classes. Gastrointestinal tolerability and genitourinary infections were the most important adverse effects of GLP1RA and of SGLT2i, respectively.

Results of our study should be considered in the light of some limitations and strengths. As for all retrospective observational studies, biases could hold in the autonomous decision of the physicians to prescribe one drug instead of the other, possibly affecting the outcomes. To mitigate this limitation, we adjusted our analysis for unbalanced baseline features. Furthermore, no data about therapeutic adherence or missing drug doses were reported in the electronic clinical charts, therefore, we are not able to assess whether a low or high compliance might affect our results. We also acknowledged the relatively short follow-up, even though the Kaplan-Meier curves do not suggest that a longer follow-up would have highlighted differences between groups, and the absence of data about urine albumin excretion in most of the study population. Finally, we collected data on concomitant therapy at baseline only, so our analysis could not assess the impact of changes in concomitant therapies on the outcomes.

Strengths of the study include the use of data from a tertiary-level diabetes unit of one of the largest hospitals in Italy, allowing the extraction of data rigorously collected by experienced diabetes specialists, and the rigorous methodology used to conduct the study. Furthermore, to the best of our knowledge, this is one of the largest real-world studies providing a head-to-head comparison between GLP1RA and SGLT2i in terms of renal outcomes in a non-Asian setting.

## Conclusions

Although acting via different molecular mechanisms, both GLP1RA and SGLT2i might have similar effects on renal disease in diabetes, as suggested by the results of our study showing no statistically significant differences between the 2 classes of drugs in a real-world setting. In this perspective, future studies should evaluate whether the concomitant combination of GLP1RA and SGLT2i should be considered in patients with T2DM at higher risk of CKD to additively protect renal function.

## Declaration of competing interest

E. Maddaloni reported personal speaker/consultancy fees from PikDare, Abbott, MTD, MSD, EliLilly, NovoNordisk, and Merck-Serono KgA and support for attending scientific meetings from Abbott and Theras. R. Buzzetti reported research grants from AstraZeneca and speaker/consultancy fees from EliLilly, Sanofi, Abbott, Vertex, NovoNordisk, Boehringer Ingheleim, AstraZeneca, Mundipharma, and Guidotti. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

## Acknowledgments

S. Bodini, S. Pieralice, L. Coraggio, and R. Amendolara collected data. S. Bodini and S. Pieralice wrote the first draft of the manuscript and contributed to data interpretation. L. D'Onofrio, C. Mignogna, and R. Risi contributed to data collection and data interpretation. M. Salducci and R. Buzzetti contributed to data interpretation and critically reviewed the manuscript. E. Maddaloni designed the study, analyzed and interpreted data and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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