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The eGFR Slope After Starting Therapy with Empagliflozin in a Cohort of Patients with Diabetes and Stage 3 CKD: Is It Really an Issue? TEMPOREALE Real-World Study

Articoli originali

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ABSTRACT

Introduction. Chronic kidney disease (CKD) is a major complication in type 2 diabetes (T2D), leading to increased cardiovascular risk. Empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), has shown cardiorenal benefits in clinical trials, but real-world data in patients with moderate CKD are limited.

Objectives. To retrospectively evaluate changes in estimated glomerular filtration rate (eGFR) following empagliflozin initiation in T2D patients with CKD (KDIGO 3A and 3B stages), focusing on the occurrence and impact of early eGFR decline ("dip") and associated metabolic outcomes and cardiovascular risk factors.

Methods. This multicenter study included adult T2D patients with eGFR 30–60 mL/min/1.73 m² who started empagliflozin between October 2023 and April 2024. Clinical parameters were collected at baseline, 1 month, and 6 months. Subgroup analyses were conducted by CKD stage and eGFR dip status (>10% decline at 1 month).

Results. Among 166 patients, 21.6% experienced an eGFR dip. Overall, eGFR increased by 2.75 mL/min/1.73m² at 6 months ($p < 0.0001$), with more pronounced improvement in non-dippers and CKD 3A patients. In dippers, eGFR partially recovered. HbA1c decreased by ~4 mmol/mol (despite use of concomitant glucose-lowering drugs decreased at empagliflozin initiation), weight by ~2 kg, and systolic blood pressure by ~4 mmHg. Empagliflozin discontinuation occurred in 4.2% of patients, mainly due to genitourinary infections.

Discussion. Empagliflozin was associated with stabilization or improvement in renal function and modest metabolic benefits in T2D patients with CKD stage 3. The eGFR dip was infrequent and transient, supporting the continued use of empagliflozin in this population in real-world settings.

KEYWORDS: type 2 diabetes, CKD, empagliflozin, eGRF dip, real-world

Introduction

Chronic kidney disease (CKD) is a pathological condition secondary to the loss of kidney function and is characterized by a slow and progressive evolution, with a reduction in estimated glomerular filtration rate (eGFR) and/or the appearance of albuminuria. CKD affects approximately 800 million people worldwide and it is associated with an increased risk of cardiovascular disease and mortality [1–3].

Cardiorenal complications are the main cause of mortality in patients with type 2 diabetes (T2D): the presence of shared cardiovascular risk factors, as well as the well-known neurohormonal activation, inflammation, and oxidative stress, may be part of the pathophysiology that explains this complex triad [4].

The management of CKD is complex due to the multifactorial nature of the disease and, in general, the aim of care is slowing its progression to avoid dialysis or kidney transplantation, responsible for a dramatic impact on quality of life, morbidity and mortality, as well as on the costs associated with renal replacement therapy [5, 6].

CKD, including its progression to end-stage renal disease, is independently associated with an increased risk of death, cardiovascular events, and hospitalization [7].

While CKD is generally considered progressive and irreversible, new evidence suggests that sodium glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) can slow or even potentially reverse certain aspects of CKD, particularly in patients with T2D [8–13].

These medications can reduce albuminuria, a key indicator of kidney damage, and improve overall kidney function. In particular, SGLT2i represent a new effective treatment option for kidney disease in patients with T2D, and its use is recommended in patients with diabetic and non-diabetic nephropathy, up to a GFR of 20 ml/min for the effect on albuminuria and the slowing of the decline in renal function [14–17].

Empagliflozin is currently regarded as one of the SGLT2 inhibitors with the most extensive evidence supporting its cardiovascular benefits, especially in lowering the risk of cardiovascular death and hospitalization due to heart failure [18, 19]. It is indicated as an adjunct to diet and exercise for the treatment of type 2 diabetes in adults and children aged 10 years and older. It can be used as monotherapy when glycemic control is inadequate and metformin is not suitable due to intolerance, or in combination with other glucose-lowering agents. It is also indicated in adults for the treatment of symptomatic chronic heart failure and for the treatment of CKD [19]. Indeed, in phase III clinical studies, empagliflozin has determined a significant reduction in the onset or worsening of kidney disease and in the relative risk of increased albuminuria compared to placebo. Therefore, the use of empagliflozin was associated with a slower progression of renal disease compared to placebo, when added to standard care. Empagliflozin was also associated with a significantly lower risk of clinically relevant renal events [19].

In addition, in a post hoc analysis of the EMPA-REG OUTCOME clinical trial, patients were divided into three groups based on the change in eGFR from baseline at four week; empagliflozin demonstrated that the decrease in eGFR, also called “eGFR dip”, which occurs soon after the start of treatment and which has often raised concerns in clinical practice as it may predispose patients to acute kidney injury, is indeed transient and did not have a significant impact on the treatment effect of empagliflozin on cardiovascular death, hospitalization for heart failure and renal disease. Even in T2D patients with more advanced renal disease and/or on diuretic therapy, despite being more likely to have a decrease in eGFR greater than 10% following treatment with empagliflozin,

the reduction in cardiovascular and renal outcomes was not altered, supporting the treatment [20].

In the EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) trial, empagliflozin reduced cardiorenal outcomes by 28% in a diverse population of over 6,000 patients with CKD, of whom over 50% without T2D [21]. Data on chronic eGFR slopes were consistent with a benefit at any eGFR or urinary albumin:creatinine ratio level, potentially delaying kidney replacement therapy by 2-27 years, depending on baseline eGFR [21].

Following pivotal trials, it is important to assess transferability of results in the real world. Therefore, we conducted an observational study to assess slopes of eGFR levels after 1 and 6 months from the first prescription of empagliflozin in our patients. A cohort of adult T2D patients with stage 3 CKD according to KDIGO definitions was identified [2]. Clinical outcomes and modifications in type 2 diabetes therapy under routine clinical practice were also evaluated. The analysis was conducted not only on the overall population of patients treated with empagliflozin during the study period, but also with a focus on two distinct stages of CKD (stage 3A and 3B, as defined by KDIGO), and based on the presence of an “eGFR dip” (defined as a reduction in eGFR greater than 10% after initiating empagliflozin therapy).

Methods

This was a multicenter, retrospective, observational, pre-post cohort study conducted in 9 Italian diabetes outpatient clinics operating in the context of the national health system.

Eligibility criteria were: age ≥ 18 years; T2D diagnosis; eGFR values ranging between 30 and 60 ml/min (corresponding to KDIGO stage 3 CKD, measured and confirmed after a minimum of 3 months; and first prescription of empagliflozin between October 2023 and April 2024; signature of informed consent for authorizing the use of retrospective data according to Italian regulations.

The decision to start treatment with empagliflozin was based on clinical judgment and was independent of the subsequent decision to include patients in the retrospective study.

Diagnosis of Latent Autoimmune Diabetes in Adults (LADA) or type 1 diabetes, active neoplasms or treatment for malignant neoplasms in the previous 5 years, previous SGLT2i treatment, and lack of signed informed consent represented exclusion criteria.

All eligible patients were consecutively identified in the electronic medical records (EMRs) of each participating center. Patient data were extracted from EMRs.

Baseline was represented by the date of the first prescription of empagliflozin. Baseline data collected included: age, sex, ethnicity, duration of T2D, eGFR, glycated haemoglobin (HbA1c), body weight, body mass index (BMI), blood pressure, lipid profile, presence of comorbidities, glucose-lowering and antihypertensive therapy before and at the start of empagliflozin.

In terms of follow-up data, information on therapy discontinuation and eGFR was collected after 1 and 6 months. After 6 months, BMI, HbA1c, blood pressure, and changes in glucose-lowering therapy were also collected.

eGFR was calculated using the CKD-EPI formula (version 2021). According to KDIGO guidelines, CKD 3A was defined as eGFR values between 45 and 59 ml/min/1.73m^2, while CKD 3B was defined as eGFR values between 30 and 44 ml/min/1.73m^2.

Statistical methods

Due to the observational nature of this study, all patients meeting the inclusion criteria in the study period were considered, and no formal sample size calculation was performed.

The primary endpoint was represented by eGFR levels after 1 and 6 months of treatment with empagliflozin, administered according to clinical practice.

Secondary endpoints included: discontinuation of treatment with empagliflozin after 1 and 6 months from the start of therapy and reasons for discontinuation, changes from baseline to 6 months in the mean levels of creatinine, HbA1c, BMI, body weight, systolic (SBP) and diastolic (DBP) blood pressure, and changes in the likelihood of being treated with specific pharmacological classes of glucose-lowering drugs from baseline to 6 months.

Descriptive data were reported as mean and standard deviation in case of continuous variables, or proportions in case of categorical variables.

Paired t-test derived from linear mixed models for repeated measurements was applied for within-group pre-post comparisons. Results were expressed as estimated mean or estimated mean difference from T0 with their 95% confidence interval (95% CI). Proportions of patients treated with specific pharmacological classes were evaluated using mixed effects models. The results were expressed as probability of being treated and as Odds Ratio (OR) with relative 95%CI, expressing the likelihood of being treated after 6 months from the start of empagliflozin as compared to baseline.

Pre-post comparisons were performed on the overall population and in different predefined subgroups representing different renal impairment profiles:

– dippers (i.e. patients with at least 10% eGFR levels reduction after 1 month from the first prescription of empagliflozin)

– non-dippers

– CKD 3A stage

– CKD 3B stage

– dippers within CKD 3A stage

– non-dippers within CKD 3A stage

– dippers within CKD 3B stage

– non-dippers within CKD 3B stage

The primary analysis regarded the population overall and by dip phenomenon. Secondary exploratory analyses were focused on the other pre-defined subgroups.

Results

Overall, 166 subjects were identified, all starting empagliflozin between October 2023 and April 2024. All patients were treated with 10 mg according to the Summary of Product Characteristics.

Baseline patient characteristics, overall and by pre-defined subgroups, are reported in Table 1. Dippers were 35 (21.1% of cases with data available). Compared to non-dippers, dippers were more often female and had a higher prevalence of hypertension. Furthermore, higher proportions of dippers vs. non-dippers were treated with ACEi or diuretics (Table 1).

Overall, 96 subjects (57.8% of those with available data) had CKD stage 3A, while 70 (42.2%) had CKD stage 3B at baseline. Compared to individuals with CKD 3A, those with CKD 3B were older on average and showed a higher use of ACE inhibitors (Supplementary Table 1).

Mean estimated eGFR significantly improved by 2.75 ml/min/1.73m^2 from baseline to 6 months in the overall population ($p < 0.0001$) (Table 2).

In the dippers' subgroup, eGFR levels decreased from 45.2 to 37.5 ml/min/1.73m^2 in the first month (p<0.0001), but then increased to 42.5 ml/min/1.73m^2 after 6 months (Table 2) (p = 0.04).

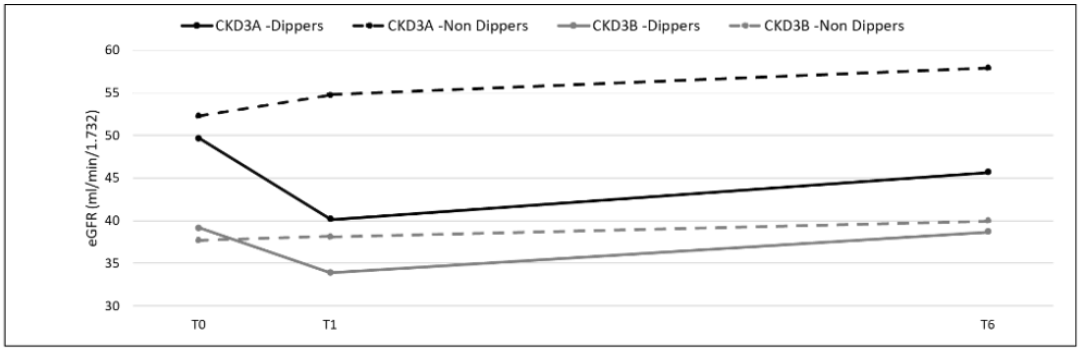
In the non-dippers' subgroup, eGFR levels increase was statistically significant both at 1 month (from 46.2 to 47.8; +1.62 ml/min/1.73m^2; p = 0.001) and at 6 months (from 46.2 to 50.5; +4.26 ml/min/1.73m^2; p < 0.0001) (Table 2).

In CKD 3A group eGFR levels significantly increased by 3.6 ml/min/1.73 m^2 after 6 months of treatment with empagliflozin (p < 0.0001), while no significant changes were documented in CKD 3B group (p = 0.30) (Supplementary Table 2).

Among patients in the CKD 3A group, 20 out of 96 (20.8%) were classified as dippers, compared with 15 out of 70 (21.4%) in the CKD 3B group. Considering the dippers group, eGFR declined by 9.5 ml/min/1.73 m^2 in CKD 3A (starting from estimated baseline levels of 49.7) and by 5.3 ml/min/1.73 m^2 in CKD 3B (starting from estimated baseline levels of 39.2) after 1 month. In both groups eGFR levels showed a partial recovery at 6 month (Figure 1). No episode of acute kidney injury occurred. Small but consistent benefits were found in terms of metabolic control: HbA1c was reduced by about 3-4 mmol/mol in all subgroups (Table 2 and Supplementary Table 2). These results were obtained in spite of the likelihood of being treated with any glucose-lowering drugs was reduced by 58% (OR = 0.42; 95%CI 0.29-0.63) (Supplementary Table 3). In more details, significant reductions in the concomitant use of metformin and sulphonylureas were documented. Trends of reduction in the prevalence of use of DPP-IVi and basal insulin was also reported. Use of GLP-1 RA was unchanged. Other classes were prescribed in less than 10% of patients before starting empagliflozin and varied marginally (Supplementary Table 3).

Regarding cardiovascular risk factors, BMI, SBP, and DBP markedly decreased after 6 months of treatment with empagliflozin, although statistical significance was not always reached due to small size of the sample. The only exception was the CKD 3B group where BMI and blood pressure were unchanged after 6 months (Table 2 and Supplementary Table 2).

Patients who discontinued empagliflozin after 1 month were 3, all for genitourinary infections. After 6 months, 4 additional patients discontinued (2 for genitourinary infections, 1 for poor compliance, 1 for hospitalization). Overall, the incidence rate of treatment discontinuation for genitourinary infections was 0.15 patient-months.



Visit	CKD3A + DIPPERS (N=20)			CKD3A + NON DIPPERS (N=74)			CKD3B + DIPPERS (N=15)			CKD3B+ NON DIPPERS (N=53)		
	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value*	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value*	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value*	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value*
T0	49.70 (47.69;51.71)			52.31 (51.27;53.36)			39.20 (37.04;41.36)			37.71 (36.57;38.86)		
T1	40.23 (36.53;43.93)	-9.47 (-12.31;-6.63)	**<.0001**	54.76 (52.84;56.69)	2.45 (0.98;3.93)	**0.001**	33.92 (31.02;36.82)	-5.28 (-7.13;-3.43)	<.0001	38.18 (36.63;39.72)	0.46 (-0.52;1.45)	0.35
T6	45.72 (41.12;50.33)	-3.98 (-7.71;-0.24)	**0.04**	57.94 (55.46;60.42)	5.63 (3.59;7.67)	**<.0001**	38.73 (35.05;42.42)	-0.47 (-3.04;2.10)	0.72	40.02 (38.11;41.94)	2.31 (1.01;3.61)	0.001

**Paired t-test derived from linear mixed models for repeated measurements. Statistically significant p-values (p<0.05) are in bold.*

Figure 1. Trend of eGFR after 1 and 6 months of therapy with empagliflozin in T2D patients according to CKD class and presence of eGRF dip.

	Overall	Dippers	Non-dippers	p-value
N	166	35	127	
Age (years)	72.6 ± 9.5	74.2 ± 7.8	72.2 ± 10.0	0.29
Sex (%):				
Men	99 (59.6)	14 (40.0)	82 (64.6)	**0.009**
Women	67 (40.4)	21 (60.0)	45 (35.4)	
Ethnicity (%):				
Caucasian	163 (98.2)	35 (100.0)	124 (97.6)	0.36
Afro-american	3 (1.8)	0 (0.0)	3 (2.4)	
T2D duration (years)	12.1 ± 9.3	14.8 ± 10.2	11.4 ± 8.9	0.05
At least 1 glucose-lowering drug (except empagliflozin) (%)	117 (70.5)	30 (85.7)	83 (65.4)	**0.02**
Median [min-max] number of glucose-lowering drugs prescribed (N)	1 [0-4]	1 [0-2]	1 [0-4]	0.18
Treated with (%):				
Diet Only	49 (29.5)	5 (14.3)	44 (34.6)	0.05
Oral Agents and/or GLP1	84 (50.6)	20 (57.1)	62 (48.8)	
Insulin	12 (7.2)	5 (14.3)	6 (4.7)	
Both	21 (12.7)	5 (14.3)	15 (11.8)	
Hypertension (%)	138 (83.1)	33 (94.3)	101 (79.5)	**0.04**
At least 1 antihypertensive drug (%)	89 (53.6)	25 (71.4)	61 (48.0)	**0.01**
Median [min-max] number of antihypertensive agents prescribed (N)	1 [0-5]	2 [0-5]	0 [0-5]	**0.006**
Treated with (%):				
ACEi	33 (19.9)	12 (34.3)	20 (15.7)	**0.01**
ARBs	40 (24.1)	8 (22.9)	30 (23.6)	0.92
Beta-blockers	37 (22.3)	11 (31.4)	24 (18.9)	0.11
Ca-antagonists	38 (22.9)	12 (34.3)	24 (18.9)	0.05
Diuretics	49 (29.5)	17 (48.6)	29 (22.8)	**0.003**
Alpha-blockers	5 (3.0)	2 (5.7)	3 (2.4)	0.31
Others	16 (9.6)	4 (11.4)	12 (9.4)	0.73
Dyslipidemia (%)	107 (64.5)	23 (65.7)	81 (63.8)	0.83
Total cholesterol (mg/dl)	163.4 ± 41.7	158.5 ± 35.1	165.8 ± 43.6	0.43
LDL-cholesterol (mg/dl)	85.2 ± 36.3	82.8 ± 32.6	86.7 ± 37.7	0.62
HDL-cholesterol (mg/dl)	47.4±12.1	49.3±13.1	47.0±11.8	0.38
Triglycerides (mg/dl)	150.4±90.8	135.9±57.9	155.0±99.2	0.32
Heart failure (%)	40 (24.1)	10 (28.6)	30 (23.6)	0.55

Table 1. Baseline characteristics. Data are mean and standard deviation, median and min-max values, or frequency and proportion. *T-test or Mann-Whitney U-test (continuous variables) or chi-square test (categorical variables).

Discussion

Consistently with clinical trials, this real-world study confirms that empagliflozin treatment in patients with T2D and stage 3 CKD is associated with a stabilization or even improvement of eGFR over six months of follow-up. eGFR dip phenomenon regards about one fifth of patients attending Italian diabetes clinics, but renal function tends to recover and improve over time, according to findings deriving from trials such as EMPA-REG OUTCOME and EMPA-KIDNEY [10, 13, 19]. In our centers, empagliflozin was associated with a significant increase in eGFR mean levels of 2.75 l/min/1.73 m^2 after 6 months. The analysis also documented that:

– the dip phenomenon was transient; after 6 months, even in these patients eGFR levels were higher than after 1 month of therapy.

– the eGFR dip was similarly frequent in the CKD 3A (21.3%) and in CKD 3B (22.1%).

– eGFR trend was similar after 6 months in the 3A and 3B KDIGO classes, despite the different mean levels recorded at baseline and at follow-up.

– eGFR trend of dippers and non-dippers was dissimilar in the two CKD classes: after 6 months, eGFR values in dippers returned to baseline levels and were similar to those of non-dippers in the CKD 3B

subgroup, whereas they remained lower than baseline and markedly lower than non-dippers in the CKD 3A subgroup.

– Mild but consistent benefits were obtained in terms of secondary outcomes: after 6 months, HbA1c was reduced by about 4 mmol/mol, weight by 2 kg, SBP by 4 mmHg, and DBP by 2 mmHg (all $p < 0.05$).

Endpoints	Visit	OVERALL (N = 166)			DIPPERS (N = 35)			NON-DIPPERS (N = 127)		
		Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value	Estimated mean levels (95%CI)	Estimated mean difference from T0 and 95% CI	p-value
eGFR (ml/min/1.73m^2)	T0	45.88 (44.63;47.14)	–	–	45.2 (42.49;47.91)	–	–	46.22 (44.8;47.64)	–	–
	T1	45.49 (43.75;47.22)	-0.4 (-1.44;0.64)	0.45	37.53 (34.05;41)	-7.67 (-9.52;-5.83)	**<0.0001**	47.84 (46.02;49.66)	1.62 (0.65;2.59)	**0.001**
	T6	48.63 (46.66;50.6)	2.75 (1.49;4)	**<0.0001**	42.57 (38.48;46.67)	-2.63 (-5.13;-0.12)	**0.04**	50.48 (48.32;52.63)	4.26 (2.93;5.58)	**<0.0001**
Creatinine (mg/dl)	T0	1.28 (1.21;1.35)	–	–	1.2 (1.05;1.35)	–	–	1.31 (1.23;1.38)	–	–
	T1	1.34 (1.27;1.41)	0.06 (0.02;0.1)	**0.006**	1.44 (1.3;1.59)	0.24 (0.16;0.33)	**<0.0001**	1.31 (1.24;1.39)	0.0 (-0.04;0.05)	0.85
	T6	1.35 (1.3;1.4)	0.07 (0;0.13)	0.05	1.45 (1.34;1.56)	0.25 (0.12;0.39)	**0.0003**	1.31 (1.25;1.37)	0.0 (-0.07;0.08)	0.89
HbA1c (mmol/mol)	T0	55.56 (53.73;57.4)	–	–	53.63 (49.67;57.6)	–	–	55.81 (53.73;57.89)	–	–
	T6	51.4 (50.09;52.71)	-4.17 (-5.57;-2.77)	**<0.0001**	50.88 (48.09;53.66)	-2.76 (-5.74;0.22)	0.07	51.4 (49.91;52.89)	-4.41 (-6;-2.82)	**<0.0001**
BMI (Kg/m^2)	T0	28.78 (28.04;29.52)	–	–	28.57 (26.97;30.18)	–	–	28.79 (27.95;29.64)	–	–
	T6	28.17 (27.43;28.92)	-0.6 (-0.96;-0.25)	**0.001**	27.61 (25.99;29.22)	-0.97 (-1.73;-0.21)	**0.01**	28.3 (27.45;29.15)	-0.5 (-0.9;-0.09)	**0.02**
Body weight (kg)	T0	79.54 (76.97;82.1)	–	**–**	77.32 (71.87;82.77)	–	–	79.81 (76.95;82.67)	–	**–**
	T6	77.42 (75.02;79.81)	-2.12 (-2.73;-1.51)	**<0.0001**	74.3 (69.21;79.38)	-3.02 (-4.32;-1.72)	**<0.0001**	77.97 (75.3;80.64)	-1.84 (-2.53;-1.15)	**<0.0001**
SBP (mmHg)	T0	134.57 (132.1;137.05)	–	–	138.86 (133.48;144.24)	–	–	133.06 (130.24;135.89)	–	–
	T6	130.62 (128.32;132.92)	-3.95 (-6.59;-1.32)	**0.003**	133.71 (128.79;138.63)	-5.15 (-10.87;0.57)	0.08	129.61 (126.99;132.22)	-3.45 (-6.48;-0.43)	**0.03**
DBP (mmHg)	T0	78.01 (76.64;79.37)	–	–	79.71 (76.75;82.68)	–	–	77.51 (75.96;79.07)	–	–
	T6	76.16 (74.66;77.66)	-1.85 (-3.61;-0.09)	**0.04**	78.62 (75.45;81.8)	-1.09 (-4.9;2.72)	0.57	75.36 (73.68;77.05)	-2.15 (-4.16;-0.13)	**0.04**

Table 2. Continuous endpoints – Results of longitudinal linear mixed models for repeated measurements – Population overall and by dip phenomenon. p-values = paired t-test derived from linear mixed models for repeated measurements. Statistically significant p-values (p < 0.05) are in bold.

Our findings suggest that patients experiencing an eGFR dip ≥ 10% within the first month of empagliflozin therapy may represent a clinically more vulnerable subgroup from a hemodynamic standpoint. In our cohort, dippers were more frequently of female gender and more frequently had hypertension. Furthermore, higher proportions of dippers vs. non-dippers patients were treated with ACEi or diuretics, i.e. factors that may reflect increased susceptibility to intraglomerular pressure shifts [19]. Nevertheless, the partial recovery of eGFR observed at 6 months in this group supports the interpretation of the dip as a functional and transient hemodynamic adjustment rather than a true renal injury. These observations highlight the importance of careful clinical assessment and monitoring in patients potentially more prone to hemodynamic fluctuations, without necessarily withholding the cardio-renal benefits of SGLT2 inhibition [19, 20].

When stratifying by CKD severity, patients with CKD stage 3A showed a statistically significant increase in eGFR, whereas those with stage 3B maintained stable kidney function without significant deterioration. These findings align with the known efficacy of empagliflozin across a broad range of baseline renal function and reinforce guideline recommendations endorsing its use down to eGFR levels of 20 mL/min/1.73m² [2, 10, 17, 22].

Beyond kidney function, empagliflozin use was associated with favourable metabolic and cardiovascular risk profiles: HbA1c was modestly but significantly reduced despite a decrease in concomitant use of other glucose-lowering agents, including metformin and sulphonylureas. It is known that in CKD, SGLT2i only modestly reduces HbA1c due to diminished effects on renal glucose excretion. Effects of SGLT2i on sodium excretion and plasma volume may be to some degree uncoupled from their glycemic effects, at least in the context of CKD [20].

Moreover, body weight and blood pressure tended to decrease, although changes were less evident in patients with more advanced CKD (stage 3B). These metabolic improvements further contribute to the cardiorenal benefits of empagliflozin observed in clinical trials [10–13].

In patients with T2D and chronic kidney disease (CKD) stage 3A or 3B, dedicated prospective clinical trials and meta-analyses reported that SGLT2i reduce SBP and DBP by a similar amount compared with patients with normal renal function [23].

In terms of implications for clinical practice, the study underlines that: it is important to start empagliflozin as early as possible, as also reported in the post hoc of EMPA-KIDNEY [21]; therapy with empagliflozin should be prescribed even if the eGFR is already reduced because it delays the progression of the decline in renal function; initial drop of eGFR regards a small proportion of patients and is generally transient [19, 20]. Furthermore, treatment discontinuation is low and mostly related to genitourinary infections, consistent with known safety profiles of SGLT2i. Importantly, no episodes of acute kidney injury were reported, even among dippers, highlighting the safety of empagliflozin in this population. Therefore, our study extends the evidence on empagliflozin's beneficial effects on renal function and metabolic control in routine clinical practice in patients with T2D and moderate CKD. This supports the integration of empagliflozin into standard care to slow CKD progression, reduce cardiovascular risk, and potentially delay the need for renal replacement therapy [24, 25].

Strengths and limitations

The main strength of this study lies in the ability to evaluate outcomes of routine clinical practice in a multicenter real-world setting, using data collected from EMRs, and to assess their consistency – or discrepancy – with evidence from randomized clinical trials.

Limitations include retrospective design, small sample size, lack of longitudinal follow-up beyond 6

months, use of potentially confounding medications, and the lack of a control group. In addition, the lack of follow-up data on albuminuria limited our ability to interpret the longitudinal results in terms of KDIGO classes. This was due to albuminuria being measured only once per year in usual care, whereas eGFR is assessed twice per year. In addition, only episodes of genitourinary symptoms resulting in treatment discontinuation were collected; less severe events were not recorded limiting the full evaluation of this important safety issue in our clinical practice. Future prospective studies with longer follow-up are warranted to confirm sustained renal benefits and to explore empagliflozin effects in more advanced CKD stages.

Conclusion

Despite reduced glucose-lowering efficacy at lower GFR levels, empagliflozin remains clinically valuable for patients with T2D and GFR between 30 and 60 ml/min/1.73m², primarily due to its proven cardiorenal protective effects. The eGFR dip phenomenon regards about one fifth of patients with CKD stage 3 and is transient, although eGFR values remain slightly lower than baseline after 6 months in patients with CKD 3A stage.

Supplementary Materials

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