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Assessing the use of sodium-glucose cotransporter 2 inhibitor in patients with type 2 diabetes mellitus and chronic kidney disease in tertiary care: a SwissDiab Study

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ABSTRACT

Introduction The overall aim of this study was to evaluate the implementation of sodium-glucose cotransporter 2 inhibitors (SGLT2i) among patients in tertiary care with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

Research design and methods The cross-sectional analysis was based on outpatients in tertiary diabetes care enrolled in the Swiss Diabetes Registry with T2DM and a study visit January 1, 2020–March 31, 2021. Prevalence of CKD was ascertained as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or persistent albuminuria as defined by Kidney Disease Improving Global Outcomes, and the proportion of patients prescribed SGLT2i was determined. Documented reasons for non-treatment with SGLT2i were extracted by a retrospective review of the medical records.

Results Of 368 patients with T2DM, 1.1% (n=4) were excluded due to missing data. Of the remaining 364 patients, 47.3% (n=172) had CKD of which 32.6% (n=56) were prescribed SGLT2i. The majority (75%) of these patients were on treatment already in 2018, before the renoprotective effects of SGLT2i were established. Among the 116 patients without SGLT2i, 19.0% had known contraindications, 9.5% stopped treatment due to adverse events, 5.2% had other reasons, and no underlying reason for non-treatment could be identified for 66.4%.

Conclusions A divergence between recommended standard of care and implementation in daily clinical practice was observed. Although treatment should always consider patient-specific circumstances, the results highlight the need to reinforce current treatment recommendations to ensure patients benefit from the best available care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinical guidelines now recommend the use of sodium-glucose cotransporter 2 inhibitors, an anti-diabetic medication with proven kidney-protective effects, in the treatment of people with type 2 diabetes and chronic kidney disease. However, implementation of new treatment recommendations in daily clinical practice often takes time.

WHAT THIS STUDY ADDS

⇒ Two in three patients with type 2 diabetes and chronic kidney disease enrolled in the Swiss Diabetes Registry did not receive treatment aligned with recommended guidelines. For a majority of these patients (66%), no underlying reason for non-treatment could be identified.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our hope is that the results of this study might motivate diabetes care providers to evaluate their own clinical practice, and relevant stakeholders (eg, medical associations, division heads and patient organizations) to take active measures to help ensure that this patient population benefit from the best available treatment.

INTRODUCTION

Around 40% of patients with type 2 diabetes mellitus (T2DM) are expected to develop chronic kidney disease (CKD).[1 2] Once established, CKD is associated with a 3-fold to 12-fold higher risk of premature death, predominantly from cardiovascular disease (CVD).[1] The condition does not remit spontaneously, and since the introduction of renin–angiotensin–aldosterone system inhibitors more than three decades ago, treatment options have remained relatively unchanged.[3–5] However, the last couple of years have seen a substantial development in renoprotective pharmacotherapy.

The renoprotective effects of sodium-glucose cotransporter 2 inhibitor (SGLT2i) observed in the cardiovascular outcome trials

published during the second half of the 2010s[6–8] were confirmed in 2019 with the CREDENCE trial, showing a 34% reduction in the relative risk of the renal-specific primary outcome in patients with T2DM and CKD, and a 20% lower relative risk of cardiovascular death, myocardial infarction, and stroke.[9] In light of these results, the European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) revised the treatment guidelines for diabetes in 2019, recommending that patients with T2DM and CKD be treated with SGLT2i.[10] Similar recommendations were included in the 2019 update of the 2018 consensus report on the management of hyperglycemia in T2DM by the American Diabetes Association (ADA) and EASD.[11] In 2020, this recommendation was adopted by the Kidney Disease Improving Global Outcomes (KDIGO) foundation and in the national treatment guidelines by the Swiss Society of Endocrinology and Diabetology.[12 13]

At the time, evidence of renoprotection had also been observed in the cardiovascular outcome trials with glucagon-like peptide-1 receptor agonists (GLP-1 RA), or secondary analysis thereof.[14–16] Although direct effects on glomerular filtration rate were unclear, data indicated beneficial effects on albuminuria and the risk of persistent macroalbuminuria, which in turn might contribute to a reduced risk of a progressive decline in renal function. In light of the current evidence, the guidelines recommend that treatment with GLP-1 RA (with proven cardiovascular benefit) should be considered for diabetes treatment if estimated glomerular filtration rate (eGFR) is >30 mL/min/1.73 m^2 and as an alternative treatment for patients with T2DM and CKD who do not qualify for or tolerate SGLT2i.[10 11]

The evidence in support of the use of SGLT2i for renoprotection in patients with T2DM and CKD is convincing. However, implementation of new treatment regimens in daily clinical practice can be slow and challenging. The primary aim of this study was to assess the implementation of SGLT2i among patients with T2DM and CKD in tertiary care enrolled in the Swiss Diabetes Registry (SwissDiab). A secondary aim was to determine the use of GLP-1 RA among patients with albuminuria and/or eGFR >30 mL/min/1.73 m^2 who were not prescribed SGLT2i . Whether certain patient-related or diabetes-related characteristics were more likely to be associated with SGLT2i was also assessed.

METHODS

Study participants

The cross-sectional study was based on SwissDiab, an ongoing multicenter longitudinal observational study of outpatients with diabetes regularly treated in tertiary diabetes care centers. The objective of SwissDiab is to assess diabetes care and management, prevalence and incidence of diabetes-related complications, and quality of life of patients, with the overall aim of providing feedback on the state of daily clinical practice to help ensure that best clinical care is provided. Patients ≥18 years of age are eligible for participation, regardless of diabetes type (gestational diabetes excluded), duration, or treatment. Patients with irregular attendance (eg, due to drug abuse or mental disorder), inability to provide informed consent, or a life expectancy <1 year due to severe comorbidity (eg, end-stage cancer) are excluded at the discretion of the attending physician. Patients enrolled in SwissDiab undergo a standardized annual health examination, where patient-related information, including medical history, diabetes-related complications, cardiovascular risk factors, biochemistry, and current medication, is collected by trained medical staff.[17] Patients are enrolled at the tertiary diabetes center at the Cantonal Hospital of St Gallen (coordinating center), and Basel, Bern, Geneva, and Zürich University Hospital.

The current study includes all patients with T2DM and a study visit between January 1, 2020 and March 31, 2021. Diabetes was defined in accordance with the recommendation by the ADA.[18] If more than one study visit was available, the most recent was used, unless missing data justified the use of a previous visit.

CKD definition

CKD was defined in accordance with KDIGO, as an eGFR <60 mL/min/1.73 m^2 and/or persistent albuminuria.[13] The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR.[19] As SwissDiab is based on annual study visits, persistent albuminuria was defined as an albumin–creatinine ratio (ACR) ≥3 mg/mmol for a minimum duration of 12 rather than 3 months.

Patients were further stratified in accordance with the KDIGO risk of CKD progression as follows: low risk, eGFR ≥60 mL/min/1.73 m^2 without albuminuria; moderately increased risk, eGFR 45–59 mL/min/1.73 m^2 or moderately increased albuminuria (ACR 3–30 mg/mmol); high risk, eGFR 30–44 mL/min/1.73 m^2 without albuminuria, eGFR 45–59 mL/min/1.73 m^2 and moderately increased albuminuria, or eGFR ≥60 mL/min/1.73 m^2 and severely increased albuminuria (ACR >30 mg/mmol); and very high risk, eGFR<30 mL/min/1.73 m^2 without albuminuria, eGFR 30–44 mL/min/1.73 m^2 and moderately increased albuminuria, or eGFR 45–59 mL/min/1.73 m^2 and severely increased albuminuria.[13]

Clinical characteristics

Weight was measured with a digital scale with patients wearing light clothes without shoes. Height was measured with a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Systolic and diastolic blood pressure were measured following a 5-minute rest with the patient in a seated position. In case blood pressure was measured on both arms, the higher finding was used. Arterial hypertension was defined as blood pressure levels above 140 mm Hg systolic and 90 mm Hg diastolic and/or treatment with antihypertensive medication. Prevalence and

history of diabetes-related complications were collected at the annual study visit by the attending physician as previously described.[20]

Information about current drug treatment was collected at the time of the SwissDiab visit and categorized based on Anatomical Therapeutic Chemical code. Finerenone was approved by the Swiss Agency for Therapeutic Products (Swissmedic) as of January 5, 2022 and was not included in the analysis. Documented reasons for non-treatment with SGLT2i or GLP-1 RA were extracted by a single reviewer based on a retrospective review of the medical records. In Switzerland, GLP-1 RA treatment is reimbursed by the health insurance for patients with a BMI ≥28 kg/m^2.

Biochemistry

Patients were instructed to arrive in a fasted state (>8 hours). ACR was determined based on random spot urine. Albumin was measured with an immunoturbidimetric assay and serum and urine creatinine with a colorimetric assay (Jaffé). Glycated hemoglobin A1c (HbA1c) was measured using National Glycohemoglobin Standardization Program-certified, International Federation of Clinical Chemistry and Laboratory Medicine traceable assays (boronate affinity chromatography and turbidimetric inhibition immunoassay). Serum triglycerides and total, high-density lipoprotein, and low-density lipoprotein (LDL) cholesterol levels were determined using enzymatic colorimetric tests according to routine methods at the center of laboratory medicine at each study center, apart from the University Hospital Zürich which routinely determines LDL-cholesterol based on the Friedewald formula.[21]

Statistical analysis

Descriptive statistics were presented as median with IQRs for continuous variables, and frequencies (%) for categorical variables. Wilcoxon rank-sum test or two-sample t-test was used to assess differences in continuous traits between patient groups as indicated. The X^2 test was used to assess differences in frequencies. Univariate logistic regression was used to determine if any of the patient characteristics were associated with SGLT2i. Patient characteristics with a p value of <0.05 were combined in a multivariable logistic regression model, additionally adjusted for age, sex and HbA1c, to determine characteristics independently associated with treatment. All analyses were performed using SAS V.9.4 (SAS Institute).

RESULTS

In total, 695 patients with diabetes had a SwissDiab visit during the study period. Of the 368 patients with T2DM, 1.1% (n=4) had to be excluded due to missing information. Of the 364 patients included in the analysis, 47.3% (n=172) had CKD, defined by reduced eGFR in 25.6% (n=44), persistent albuminuria in 41.3% (n=71), or both reduced eGFR and persistent albuminuria in 33.1% (n=57) of cases. According to the KDIGO risk stratification, 49.4% (n=85) of the patients were at moderately increased risk, 26.7% (n=46) at high risk, and 23.8% (n=41) at very high risk of CKD progression. Clinical characteristics are presented in table 1, further stratified by current treatment with SGLT2i.

Patients with CKD and SGLT2i treatment

Of the 172 patients with CKD, 32.6% (n=56) were prescribed SGLT2i. Stratified by risk of CKD progression, 37.6% (n=32) of patients at moderate risk, 32.6% (n=15) of patients at high risk, and 22.0% (n=9) of patients at very high risk were prescribed SGLT2i. A more detailed distribution of patients based on risk of CKD progression according to the KDIGO classification and the proportion in each category with SGLT2i is provided in online supplemental figure 1.

Of the 56 patients with SGLT2i, 75.0% (n=42) were on treatment already in 2018, that is, prior to the publication of the ESC/EASD guideline in August 2019 that for the first time recommend treatment with SGLT2i for patients with T2DM and CKD.[10] Of the remaining 14 patients, 7 were initiated on SGLT2i after August 2019, of which 71.4% (n=5) had the specific indication of renal protection mentioned in the patient record and the remaining 28.6% (n=2) improved glycemic control in combination with cardiovascular risk reduction.

Patients with CKD without SGLT2i treatment

Reasons for non-treatment with SGLT2i as identified by patient characteristics (eg, eGFR <30 mL/min/1.73 m^2) or as documented in the patient records are presented in table 2.

Of the 116 patients who were not prescribed SGLT2i, 101 had an eGFR >30 mL/min/1.73 m^2 of which 42.6% (n=43) were prescribed GLP-1 RA. Of the 13 patients for which treatment with GLP-1 RA was initiated after August 2019, 1 patient (7.7%) had the specific indication of cardiorenal protection documented in the patient record, and 1 patient (7.7%) cardiovascular protection. The available information was unclear for one patient, whereas weight and/or glycemic control was indicated for the remaining patients.

Of the 101 patients with eGFR >30 mL/min/1.73 m^2, 83 had a BMI >28 kg/m^2 of which 48.2% (n=40) were prescribed GLP-1 RA. Of the 43 patients who were not prescribed GLP-1 RA, 1 patient declined treatment due to fear of needles and 8 (18.6%) had stopped treatment during 2018 or earlier (one patient developed pancreatitis, one patient due to adverse event, five patients due to diminished effect on weight and glycemic control, one patient for unclear reasons). Three patients could not be properly assessed, and no reason could be identified for 31 patients (72.1%), of which 23 (74.2%) showed consistently good glycemic control under current antidiabetic treatment as noted by the treating physician.

Of the 101 patients with eGFR >30 mL/min/1.73 m^2, 72 patients had persistent albuminuria (48.6% prescribed

Table 1 Characteristics of SwissDiab patients with T2DM, overall and with CKD, the latter further stratified by treatment with SGLT2i

Characteristics	Patients with T2DM (n=364)	Patients with T2DM and CKD			P value*
		All (n=172)	With SGLT2i (n=56)	Without SGLT2i (n=116)	
Age, years	65.7 (58.2–72.7)	69.0 (63.3–75.2)	66.0 (59.8–75.0)	69.5 (64.7–75.4)	0.03
Females, no (%)	95 (26.1)	43 (25.0)	14 (25.0)	29 (25.0)	1.00
Diabetes duration, years	14.0 (8.0–21.0)†	18.0 (11.5–25.0)	16 (9–23)	18 (13–25)	0.16
Smokers, no (%)	71 (19.5)	29 (16.9)	11 (19.6)	18 (15.5)	0.50
HbA1c, %	7.2 (6.5–7.9)‡	7.3 (6.7–8.2)‡	7.5 (6.9–8.2)	7.2 (6.7–8.2)‡	0.14
HbA1c, mmol/mol	55 (48–63)‡	56 (50–66)‡	58.5 (51.9–65.6)	55.2 (49.7–66.1)‡	0.14
BMI, kg/m^2	30.4 (27.6–34.4)†	30.8 (28.2–35.1)	30.7 (27.4–36.0)	30.8 (28.6–34.7)	0.63
BMI >28 kg/m^2, no (%)	261 (71.7)	133 (77.3)	39 (69.6)	94 (81.0)	0.09
SBP, mm Hg	133 (122–145)†	135 (126–147)	136 (124–146)	134 (127–149)	0.70
DBP, mm Hg	80 (74–85)†	79 (74–83)	79 (74–85)	79 (74–83)	0.83
Hypertension, no (%)	295 (81.0)	166 (96.5)	54 (96.4)	112 (96.6)	0.97
Total cholesterol, mmol/L	3.9 (3.3–4.7)†	3.8 (3.3–4.7)†	3.8 (3.4–4.8)	3.8 (3.2–4.7)†	0.56
Triglycerides, mmol/L	1.7 (1.2–2.4)	1.9 (1.3–2.9)	2.1 (1.4–2.9)	1.8 (1.2–2.6)	0.22
HDL-cholesterol, mmol/L	1.1 (1.0–1.3)†	1.1 (0.9–1.3)†	1.1 (0.9–1.2)	1.1 (0.9–1.3)†	0.16
LDL-cholesterol, mmol/L	2.4 (1.9–2.9)†	2.3 (1.9–2.9)†	2.4 (2.1–3.0)	2.3 (1.8–2.8)†	0.13
Retinopathy, no (%)	53 (14.6)†	33 (19.3)†	7 (12.7)†	26 (22.4)	0.13
Neuropathy, no (%)	202 (55.5)	123 (71.5)	36 (64.3)	87 (75.0)	0.14
CVD, no (%)	124 (34.1)	78 (45.4)	24 (42.9)	54 (46.6)	0.65
eGFR, mL/min/1.73 m^2	78.6 (56.7–95.0)†	55.0 (44.3–80.0)	63.3 (52.3–84.0)	50.4 (39.4–76.8)	0.002
ACR, mg/mmol	2.2 (1.1–8.6)§	8.4 (3.3–24.8)¶	8.4 (5.2–26.4)**	8.2 (2.6–24.8)††	0.25
CKD definition, no (%)					0.07‡‡
Reduced eGFR	–	44 (25.6)	9 (16.1)	35 (30.2)	0.05
Persistent albuminuria	–	71 (41.3)	29 (51.8)	42 (36.2)	0.05
Both	–	57 (33.1)	18 (32.1)	39 (33.6)	0.85
KDIGO risk stratification, no (%)					0.21‡‡
Low	191 (52.5)	–	–	–	–
Moderately increased	85 (23.4)	85 (49.4)	32 (57.1)	53 (45.7)	0.16
High	46 (12.6)	46 (26.7)	15 (26.8)	31 (26.7)	0.99
Very high	41 (11.3)	41 (23.8)	9 (16.1)	32 (27.6)	0.10
Medication, no (%)					
Insulin	227 (62.4)	127 (73.8)	50 (89.3)	77 (66.4)	0.001
Metformin	267 (73.4)	115 (66.9)	46 (82.1)	69 (59.5)	0.003
Classic OADs	289 (79.4)	127 (73.8)	48 (85.7)	79 (68.1)	0.01
Antihypertensives	295 (81.0)	166 (96.5)	54 (96.4)	112 (96.6)	0.97
RAASi	268 (73.6)	153 (89.0)	52 (92.9)	101 (87.1)	0.26
SGLT2i	138 (37.9)	56 (32.6)	56 (100)	–	–
GLP-1 RA	107 (29.4)	52 (30.2)	5 (8.9)	47 (40.5)	0.00002

If not otherwise specified, data are median values with IQR in brackets.
*Comparing patients with and without SGLT2i using Wilcoxon rank-sum test for continuous variables and X^2 test for categorical variables.
†Information missing for one patient.
‡Information missing for two patients.
§Information missing for 40 patients.
¶Information missing for 23 patients.
**Information missing for six patients.
††Information missing for 17 patients.
‡‡X^2 test, 2×3 contingency table.
ACR, albumin–creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; KDIGO, Kidney Disease Improving Global Outcomes; LDL, low-density lipoprotein; OADs, oral antidiabetic drugs (sulfonylurea, biguanides, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors); GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAASi, renin–angiotensin–aldosterone system inhibitors; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SwissDiab, Swiss Diabetes Registry; T2DM, type 2 diabetes mellitus.

Table 2 Identified reasons for non-treatment with SGLT2i

Identified reasons for non-treatment with SGLT2i	
Contraindications	
eGFR <30 mL/min/1.73 m^2	15 (12.9%)
Adverse events	11 (9.5%)
Kidney transplant	7 (6.0%)
Other	
Patient/GP related	6 (5.2%)
No reason identified	77 (66.4%)

Data presented are frequency (%).
eGFR, estimated glomerular filtration rate; GP, general practitioner; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

GLP-1 RA) of which 60 patients also had a BMI >28 kg/m^2 (53.3% prescribed GLP-1 RA).

Patient characteristics associated with SGLT2i treatment

Treatment with insulin, metformin and classic oral antidiabetics (sulfonylurea, biguanides, alpha-glucosidase inhibitors and dipeptidyl peptidase-4 inhibitors), respectively, and eGFR were positively associated with SGLT2i treatment (online supplemental table 1). Treatment with insulin (OR=4.70, 95% CI (1.80, 12.27)) and metformin (OR=2.61, 95% CI (1.09, 6.25)) remained independently associated with SGLT2i in a multivariable model. As metformin constitutes a large proportion of classic oral antidiabetics, and the OR and p value for metformin were stronger than that observed for classic oral antidiabetics in the univariate analysis, the latter was excluded from the multivariable model. Adjusting for age, sex and HbA1c did not materially change the results (data not shown).

DISCUSSION

CKD was identified in 47% of the patients with T2DM in tertiary care and a divergence between recommended treatment guidelines and current daily clinical practice was observed. One in three patients was prescribed SGLT2i with proven renal protective effects, and no documented reason for non-treatment could be identified for 66% of the patients without treatment. Of the patients not prescribed SGLT2i but eligible for treatment with GLP-1 RA, less than half (48%) were treated, and 11% had documented reasons for non-treatment.

In general, no evidence of SGLT2i being preferentially prescribed was observed. That eGFR was positively associated with SGLT2i is partly explained by the treatment limitation (at the time, eGFR >30 mL/min/1.73 m^2). Patients with insulin treatment were also more likely to be prescribed SGLT2i. Given that glycemic control was overall good, and that patients with SGLT2i tended to have a higher HbA1c than patients without, suggest that SGLT2i was more likely to be prescribed on top of traditional antidiabetic medication in response to insufficient glycemic control. This is further supported by the vast majority of patients being on treatment already in 2018, that is, prior to the renoprotective effect of SGLT2i being fully established, indicating that improved glycemic control rather than renal protection was the main indication behind the prescription.

That renal protection was specifically indicated for the majority (71%) of patients who started SGLT2i treatment after August 2019 is encouraging. Similar tendencies were observed in a study by Harris *et al*, looking at prescription trends of antidiabetic medication among patients with T2DM and CKD in the USA.[22] The study was based on 160 489 patients enrolled in commercial and Medicare Advantage insurance plans for whom a new antidiabetic treatment was initiated between 2013 and the first quarter of 2020. A steady increase in new prescriptions of SGLT2i over time was observed, but information about the underlying indication was unavailable. However, the mean (SD) HbA1c was relatively high at initiation (8.0 (1.8)%), and a simultaneous decline in initiation of insulin therapy was observed (from 26% to 15%), and the most common prescriber specialty (in general >70% of the prescriptions up until 2019) were internists including general practitioners rather than endocrinologists, implying that improved glycemic control was the primary indication. Interestingly, the number of new prescriptions of SGLT2i among endocrinologists (and nephrologists but from a very low level) started to rise sharply in the first quarter of 2019 with a corresponding decline among internists. This coincided with the approved threshold of eGFR for SGLT2i treatment being reduced to 30 mL/min/1.73 m^2, suggesting increased prescription of SGLT2i by endocrinologists/nephrologists for reasons of cardiorenal protection.

Similar general trends were observed in a study by Gregg *et al*, based on a national sample of US veterans with T2DM, CKD and atherosclerotic CVD with a primary care visit during 2020.[23] Patients were generally older compared with the patients in the current study (72.0±6.9 years vs 66.5±10.5 years among patients with SGLT2i and 75.9±8.1 years vs 69.7±9.3 years among patients without), were predominantly male (98%), and >80% had ischemic heart disease. Of the 174 443 patients included, 11.5% were prescribed SGLT2i. Comparing patients with and without SGLT2i, 42% and 22%, respectively, had HbA1c >8.0% and 23% and 53% an HbA1c <7%, with 61% as compared with 39% being treated with insulin, suggesting that improved glycemic control was the primary indication for treatment. Patients with more tertiary care visits (to, for example, cardiologist or endocrinologist) were more likely to be treated with SGLT2i, which is in line with the trend seen in Harris *et al*, and the comparatively higher proportion of patients on treatment with SGLT2i in the tertiary setting of the current study.

The patients in the current study are very well characterized with annual study visits. In both Harris *et al* and Gregg *et al*, CKD was only defined by eGFR and was thus based on a more restricted set of patients as compared

with the current study. It is unclear how this might have influenced the results. Albuminuria is an important indicator of CKD progression and is traditionally a more well-established early sign of diabetic nephropathy than reduced eGFR, and a strong predictor of cardiorenal outcomes in diabetes management. As such, the presence of albuminuria, rather than reduced eGFR, might be more likely to lead to appropriate changes to current pharmacological treatment in daily clinical care.

From this and the other studies, it is clear that a majority of patients with T2DM and CKD are not treated with SGLT2i. Adverse events might be one reason for non-treatment, genitourinary tract infection being the most common.[24] In our study, roughly 1 in 10 patients had discontinued SGLT2i treatment due to adverse events (mainly genitourinary infections). For GLP-1 RA, the most common reported adverse events are gastrointestinal and mainly nausea, which occurs in up to 40% of users.[25–27] However, these effects are usually mild to moderate and transient, often limited to the initial titration period, and do not generally lead to drug discontinuation. In the current study, one of the patients eligible for GLP-1 RA had a documented adverse event leading to withdrawal (injection site reaction). Taken together, it is unlikely that adverse events meaningfully contributed to the observed lack of treatment with SGLT2i or GLP-1 RA.

Clinical inertia is another likely contributing factor, which is often recognized in connection with more transformative changes to daily clinical practice.[28] Inertia has multiple drivers, and has been broadly divided into provider related, patient related and health system related.[29] For physicians, personal experience is often essential to consolidate confidence prescribing newly introduced medications.[28] Both physicians and patients might be reluctant to change established treatment regimens, particularly if good glycemic control is already obtained. Last but not least, healthcare systems limit implementation by controlling insurance coverage. Health insurance is mandatory in Switzerland and generally covers SGLT2i if indicated. However, GLP-1 RA is restricted to patients with a BMI above 28 kg/m^2, which automatically rendered 23% of the patients in the current study ineligible for treatment, with the option of having to pay a rather expensive treatment out of pocket. This raises the question of economic equality in care.[12]

With new treatment options available, guidelines on T2DM management have evolved to target overall cardiovascular morbidity and mortality rather than glycemic control in isolation. However, around 8% of the patients with T2DM and CKD in the current study had documented reasons for non-treatment with both SGLT2i and GLP-1 RA. The 2022 consensus report by KDIGO and the ADA now recommend that SGLT2i be initiated if eGFR ≥20 mL/min/1.73 m^2 and can be continued until dialysis or transplant as long as tolerated by the patient.[30] These recommendations will increase the number of patients who qualify for SGLT2i. As for GLP-1 RA, the kidney outcomes trial with semaglutide (FLOW) was discontinued ahead of time end of last year due to efficacy.[31] The primary outcome consisted of five components: onset of persistent ≥50% reduction in eGFR, onset of persistent eGFR <15 mL/min/1.73 m^2, initiation of chronic kidney replacement therapy, and death from kidney or cardiovascular disease. Based on the company announcement released March 5 this year (no 20/2024), the analysis showed a 24% reduction in kidney disease progression as well as cardiovascular and kidney death in participants with T2DM and CKD as compared with placebo. Superiority was also shown for the secondary outcomes including annual rate of change in eGFR. In light of these results (although not yet published), it seems likely that the indications for semaglutide will extend. Results from a recently published study furthermore indicate an additive renoprotective effect of combining treatment with SGLT2i and GLP-1 RA. Emulating a randomized controlled trial based on national data sources, treatment with SGLT2i on top of GLP-1 RA was associated with a 57% lower risk of serious renal events (HR=0.43, 95% CI (0.23, 0.80)) as compared with treatment with GLP-1 RA alone. A less clear additive effect of GLP-1 RA on top of SGLT2i was observed (HR=0.67, 95% CI (0.32, 1.41)).[32] These results indicate that the available treatment options for this patient population have the potential to improve even further.

Strengths and limitations

A strength of this study is the real-world clinical setting, providing the opportunity to assess the implementation of SGLT2i (and GLP-1 RA) in line with current treatment recommendations in a tertiary care patient population. The time frame might have limited the study. The guidelines recommending SGLT2i were published in August 2019, leaving roughly 1–1.5 years for general physicians and endocrinologists to modify medical treatment accordingly. Another limitation is the retrospective review of reasons for non-treatment with SGLT2i and GLP-1 RA. As part of daily clinical practice, the medical records lack a standardized reporting practice, specifically with respect to capturing reasons for non-treatment with SGLT2i/GLP-1 RA. As such, the identified reasons for non-treatment are likely underestimated, specifically in terms of patient/physician-related reasons.

The observed prevalence of CKD among SwissDiab patients with T2DM is in line with current literature. 15 years after diagnosis, albuminuria is seen in 30–40% (the median (IQR) diabetes duration among the SwissDiab patients was 18 (11.5–25.0) years), and an eGFR <60 mL/min/1.73 m^2 in 30% of patients with T2DM. A previous single-center study showed that SwissDiab patients with T2DM (n=358) had longer diabetes duration and better glycemic control compared with non-participating patients (n=474), whereas no significant difference in the prevalence of nephropathy was observed.[20] The results indicate that it is unlikely that the current study is significantly overestimating or underestimating the true prevalence of CKD in this patient population. However, given

that SwissDiab is based on patients in tertiary diabetes care in the German-speaking part of Switzerland, the study is likely overestimating the prevalence of CKD in patients with T2DM in general, and patients treated in primary care in particular. Duration of diabetes is an independent risk factor for the development and progression of renal impairment[33] and patients who receive their T2DM care in a primary care setting tend to have a shorter diabetes duration and/or less established diabetes-related complications as compared with outpatients in tertiary care.[34] However, considering that CKD often remains undiagnosed until a progressive stage has already been established, early detection is paramount. A considerable variation in consistency of renal function assessment in patients at risk in general practices in Switzerland has been shown,[35] indicating a need to improve awareness of the importance of CKD detection and treatment among all levels of healthcare.

In conclusion, the results show a divergence between recommended treatment guidelines and current daily clinical care among patients with T2DM and CKD in tertiary care enrolled in SwissDiab. This indicates that major changes to clinical practice take time to implement, and active measures should be considered by relevant stakeholders (eg, medical associations, division heads, and patient organizations) to help accelerate the implementation of current treatment recommendations in daily clinical practice, to ensure patients benefit from the best treatment available.

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