Diabetes Epidemiology and Management 13 (2024) 100184

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Review

Real-life underuse of SGLT2 inhibitors for patients with type 2 diabetes at high cardiorenal risk

André J. Scheen[a,b,*]

[a] Division of Clinical Pharmacology, Centre for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium
[b] Division of Diabetes, Nutrition and Metabolic Disorders, CHU Liège, Liège, Belgium

ARTICLE INFO

Article History:
Received 12 October 2023
Accepted 17 October 2023
Available online 18 October 2023

Keywords:
Atherosclerotic cardiovascular disease
Chronic kidney disease
Gliflozin
Heart failure
Real-life
SGLT2 inhibitor

ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) and chronic kidney disease (CKD) are major complications of type 2 diabetes (T2DM). The objectives of preventing these complications are not fully reached in clinical practice. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have proven their efficacy in reducing major cardiovascular events, diminishing hospitalization for HF and limiting the progression of CKD to end-stage kidney disease in placebo-controlled randomised trials in high-risk patients with T2DM. These evidence-based benefits were confirmed in real-life cohort studies worldwide compared with other glucose-lowering agents. However, real-world data showed that only a minority of eligible patients with T2DM received an SGLT2i, yet encouraging increase was observed in recent years. Surprisingly, in several studies less patients with comorbidities (especially CKD) were treated with SGLT2is compared with T2DM patients without these complications. Bridging the gap between evidence-based cardiorenal protection with SGLT2is and their underuse in daily clinical practice in patients with T2DM at high risk is crucial from a public health viewpoint. Multifaceted and coordinated interventions involving all actors should be implemented to incite the adoption of SGLT2is as part of routine cardiovascular and renal care among patients with T2DM at high risk for these comorbidities.

Introduction

Patients with type 2 diabetes mellitus (T2DM) [1] are exposed to a high risk of atherosclerotic cardiovascular disease (ASCVD) [2], heart failure (HF) [3] and chronic kidney disease (CKD) [4]. Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) have proven their efficacy in reducing the incidence of major cardiovascular adverse events (MACEs: a composite of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke) in high-risk patients with T2DM [2,5]. This cardioprotective effect was observed in placebo-controlled cardiovascular outcome trials (CVOTs) in patients who were at high cardiovascular (CV) risk (most patients with established ASCVD) [6,7]. It was also confirmed in retrospective observational cohort studies that compared outcomes with SGLT2is versus other glucose-lowering agents, especially dipeptidyl peptidase-4 inhibitors (DPP-4is or gliptins), including among patients in primary prevention [8]. Importantly, SGLT2i therapy was associated with a significant and highly reproducible reduction in hospitalization for heart failure (hHF) [3], a remarkable effect reported in placebo-controlled CVOTs in patients with either HF with reduced ejection fraction (HFrEF), mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF) [6,7,9]. This benefit was confirmed in observational retrospective cohort studies [8,10,11], thus moving from efficacy in CVOTs to effectiveness in real-world [7,12]. Finally, nephroprotective effects have also been consistently reported with SGLT2is in patients with T2DM and CKD. These agents were associated not only with a significant reduction in urinary albumin-creatinine ratio (UACR), but also, and more importantly, in the progression to end-stage kidney disease (ESKD) in patients with reduced estimated glomerular filtration rate (eGFR) [4,13,14].

These favourable evidence-based results [15,16] led to a privileged positioning of SGLT2is in international consensus reports for the management of patients with T2DM at high risk by diabetologists [17,18] cardiologists [19] and nephrologists [20]. According to the 2019 ADA-EASD (American Diabetes Association/European Association for the Study of Diabetes) guidelines and 2019 ESC (European Cardiology Society) guidelines, 37.2 % of patients among 435 000 patients with T2DM identified from the Swedish National Diabetes Register (2020−21) were recommended treatment with SGLT2is, but only 27.0 % were treated with these medications [21]. The US National Health and Nutrition Examination Survey from 2017 to 2018 showed substantial gaps in the use of SGLT2is despite a large

* Correspondence to: Division of Clinical Pharmacology, Centre for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium.
E-mail address: andre.scheen@chu.ulg.ac.be

https://doi.org/10.1016/j.deman.2023.100184

number of patients being eligible for guideline−recommended cardiorenal protective therapies [22]. A recent international cohort study showed that sulphonylureas remain the most common second-line medications prescribed following metformin in both the United States and the United Kingdom and that the use of newer glucose-lowering therapies with cardiovascular benefits remains low despite recommendations [23]. Addressing this paradox may help reduce the morbidity and mortality associated with ASCVD, HF and CKD among patients with T2DM [24].

The present comprehensive review analyzes the gap between, on the one hand, clinical evidence emerging form placebo-controlled randomised clinical trials (RCTs), which consistently showed cardiorenal benefits that were confirmed in retrospective observational studies comparing SGLT2i users versus non-users and, on the other hand, the relatively low use of SGLT2is in daily practice in the US and worldwide among patients with T2DM, especially those with antecedents of ASCVD, HF and/or CKD. In a first step, results of meta-analyses of RCTs and retrospective observational cohort studies were briefly summarized. They evidenced a significant reduction of MACEs, hHF and renal outcomes associated with SGLT2is versus placebo or other glucose-lowering agents used as active comparators. In a second step, observational studies in real-life conditions which reported the proportion of patients with T2DM treated with SGLT2is among a population that deserved such protective agents because of the presence of ASCVD, HF or CKD. Findings underlined underuse of SGLT2is in clinical practice among patients with T2DM who should benefit of this therapy [25].

The main reasons for such a gap between evidence-based data demonstrating clear-cut CV and renal benefits with SGLT2is and the underuse of these protective agents in daily clinical practice as well as the different approaches that could contribute to bridge this gap have been extensively discussed in another recent article [26] and will only briefly summarized here.

Demonstration of cardiovascular and renal protection

Placebo-controlled CVOTs

A network meta-analysis of 23 CVOTs concluded that SGLT2is are superior to DPP-4is in reducing the risk of most CV (and renal) outcomes and are superior to GLP-1RAs in reducing the risk of hHF (and renal) events [27].

Patients with ASCVD

In a meta-analysis of ten RCTs in patients with ASCVD (25,108 patients in the SGLT2i group and 18,574 patients in the placebo group), SGLT2i treatment significantly reduced CV mortality (relative risk [RR] 0.85, 95 % confidence interval [CI] 0.79−0.92; $P < 0.0001$) and even more hHF (RR 0.69, 0.64−0.81; $P < 0.00001$) [28]. In a meta-analysis of 5 RCTs comprising 23 987 patients with T2DM patients but without established ASCVD (primary prevention), the use of SGLT2is led to significant reductions in MACEs (RR, 0.74, 95 % CI, 0.61−0.89; $P = 0.001$), myocardial infarction (RR 0.67, 0.47−0.97; $P = 0.03$), and stroke (RR, 0.61, 0.41−0.91; $P = 0.01$) primarily in patients with CKD along with T2DM, whereas these benefits failed to reach statistical significance in patients with T2DM without CKD [29]. Another meta-analysis of 10 RCTs confirmed that the clinical benefits with SGLT2is such as preventing CV death, HF worsening, or stroke may be greater for patients with more severe CKD [30].

Patients with HF

In patients with HF, a meta-analysis of seventeen RCTs, comprising a total of 20,749 participants, ($n = 10,848$ treated with SGLT2is and $n = 9901$ treated with a comparator) showed that treatment with SGLT2is was associated with 32 % relative risk reduction (RRR) of hHF (RR 0.68, 95 % CI 0.62−074), and 18 % RRR of CV mortality (RR 0.82, 0.73−0.91) [31]. A meta-analysis of nineteen RCTs, including 20 633 patients with HF and an ejection fraction of 40 % or more showed that SGLT2is were associated with a significant reduction in the risk of hHF compared with placebo (HR 0.71, 95 % CI 0.60−0.83] [32]. As this reduction was greater than that observed with other drugs, these findings suggest that SGLT2is are the optimal drug class for HFpEF and HFmrEF as compared with other cardiological drugs classically used for the treatment of HFrEF.

Patients with CKD

A first systematic review and meta-analysis of four studies with a total of 38 723 participants published in 2019 assessed the effects of SGLT2is on major kidney outcomes in patients with T2DM. SGLT2is substantially reduced the composite risk of dialysis, transplantation, or death due to CKD (RR 0.67, 95 % CI 0.52−0.86; $P = 0.0019$). They also reduced ESKD (0.65, 0.53−0.81; $P < 0.0001$), and acute kidney injury (0.75, 0.66−0.85, $P < 0.0001$). Benefits were consistent across studies, including for participants with a baseline eGFR 30−45 mL/min per 1.73 m^2 and irrespective of baseline albuminuria [13]. A more recent collaborative meta-analysis identified 13 large placebo-controlled RCTs with 90 409 participants (82.7 % participants with diabetes) who had a mean baseline eGFR ranging between 37 and 85 mL/min per 1.73 m^2). Compared with placebo, allocation to an SGLT2i reduced the risk of kidney disease progression by 37 % (RR 0.63, 95 % CI 0.58−0.69). SGLT2is reduced the risk of acute kidney injury by 23 % (0.77, 0.70−0.84), the risk of CV death or hHF by 23 % (0.77, 0.74−0.81) and the risk of CV death by 14 % (0.86, 0.81−0.92), all differences highly statistically significant. Interestingly, similar effects were observed in people with and without diabetes and irrespective of trial mean baseline eGFR [14].

Overall, the conclusion of placebo-controlled trials is that in a population of individuals with T2DM and a high CVD and/or renal risk, both CV and renal benefits of SGLT2is are substantial, whatever the baseline characteristics with a apparent greater benefit in patients with more severe comorbidities, especially CKD. Despite the possible occurrence of some adverse effects [33], the benefit-risk ratio of SGLT2is is favourable [34].

Observational real-life studies

Several meta-analyses of observational studies that investigated the effect of SGLT2is versus DPP-4is or any other glucose-lowering agents on CV events, mortality, hHF and renal events were published in recent years. CV and renal outcomes with SGLT2is in real-life observational studies in older patients with T2DM were discussed in a recent paper [35].

In a meta-analysis of fourteen observational and cohort studies enrolling 3 157,259 patients, SGLT2is compared to other glucose-lowering drugs reduced MACEs (odds ratio [OR] 0.71, 95 % CI 0.67−0.75; $P < 0.001$), CV mortality (OR 0.58, 0.49−0.69; $P < 0.001$), myocardial infarction (OR 0.77, 0.73−0.81; $P < 0.001$), stroke (OR 0.75, 0.72−0.78; $P < 0.001$), and the risk of hHF (OR 0.56, 0.46−0.68; $P < 0.001$) [36].

A meta-analysis focusing on cerebrovascular outcomes selected 20 observational studies with SGLT2is, of which thirteen considered the comparison with DPP-4is and seven the comparison with non-SGLT2i glucose-lowering agents. The pooled intention-to-treat analysis showed a reduced risk of stroke with SGLT2is compared to DPP-4is (HR 0.89, 95 % CI, 0.82−0.96) and non-SGLT2i anti-hyperglycemic medications (HR 0.83, 0.77−0.91) [37].

A meta-analysis of RCTs ($N = 34,322$), observational studies ($N = 1$ 536,339), and both ($N = 1$ 570,661) demonstrated a significant reduction in hHF (OR 0.70, 0.64, 0.66; all $P = 0.0001$) with SGLT2is

compared to placebo (RCTs) or other anti-diabetes drugs (observational studies) in patients with T2DM [38]. Interestingly, this work showed no difference between the results of RCTs and those of observational studies. In another meta-analysis of 21 observational studies, SGLT2is were associated with a reduced risk of hHF (HR 0.65, 95 % CI 0.59−0.72) overall and both in those with ASCVD (HR 0.78, 0.68 −0.89) and without ASCVD (HR 0.53, 0.39−0.71). Absolute risk reduction for hHF in people with a history of CVD was significantly greater than in those without ASCVD, corresponding to different number-needed-to-treat values to prevent one event of hHF, 86 person-years and 256 person-years, respectively [39]. Thus, real-world SGLT2i use supports RCT data for the size effect of reduced hHF in patients with T2DM, although with a much lower absolute risk reduction in people without CVD.

In a meta-analysis of 20 observational studies across 15 countries with a total population of 1 494 373, SGLT2is were associated with a 46 % lower risk of kidney failure events (comprising kidney transplantation, maintenance dialysis, death from kidney failure, sustained eGFR <15 mL/min per 1.73 m^2 or sustained ≥ 40 % decline in kidney function) compared with other glucose-lowering drugs (HR 0.54, 95 % CI 0.47−0.63). This finding was independent of baseline eGFR or albuminuria status [40], thus confirming results from placebo-controlled RCTs [13,14,41]. Thus, there is definitely a place for SGLT2is to prevent CKD in clinical practice, yet challenges remain that should be overcome to progressively increase their use [42−44].

Underuse of SGLT2is among high-risk patients in clinical practice

Table 1 summarizes the findings about the use of SGLT2is among patients with T2DM and comorbidities (ASCVD, HF, CKD) that should make them eligible for a treatment with SGLT2is and who received this treatment in real-world observational studies [22,45−63]. In total, 20 studies were identified after a careful scrutinization of the international literature. Most studies were carried out in the United States. ASCVD is defined by antecedents of a CV event (mainly coronary artery disease and stroke) or a procedure of revascularization. HF essentially concerned HFrEF, the first type of HF which was validated for SGLT2i use. The definition of CKD was based upon the presence of a reduced eGFR or of albuminuria (Table 1). Overall, most studies reported percentages of patients with T2DM and comorbidities treated with SGLT2is comprised between 6.0 and 28.0 %, except in a Korean study in patients with CKD (32.9 %) [48] and another small-size study performed in India (3.1 %) [63]. The findings of a recent Swedish study that recruited patients with HFrEF and reported much higher use of SGLT2is (69.8 % in 2022) [61] are discussed below. No obvious differences in the underuse of SGLT2is could be detected across the type of comorbidity, even if a trend for a lower use seems apparent in patients with CKD compared to those with ASCVD or HF (Table 1).

Some studies reported a trend of use of SGLT2is throughout the duration of the study, from 2013 to 2020, and all showed a significant, yet still insufficient, increase with time [46,47,52,56,58−61]. This was also reported in DISCOVER, a global, prospective, observational study among 14,576 patients with T2DM from 37 countries, 8.7 % were started on an SGLT2i at enrollment (2014−16) and an encouraging, yet limited, increase up to 12.8 % was noticed at end of follow-up three years later [64]. Of note, in contrast to observational studies collected in Table 1, patients with T2DM of the DISCOVERY were not recruited because of the presence of comorbidities such as ASCVD, HF or CKD [64]. One recent study that collected data from the Swedish Heart Failure Registry in patients with HFrEF reported much higher and increasing levels of use of SGLT2is (from 46.2 % to 69.8 %) among patients with T2DM registered between 1 November 2020

Table 1
Use of SGLT2is in T2DM patients with ASCVD, HF or CKD in real-life.

Refs.	Country	n	Comorbidity	% use (starting year)	% use (late year)
Atherosclerotic cardiovascular disease (ASCVD)					
Arnold et al. [45]	US	5006	ASCVD (coronary artery, cerebrovascular, or peripheral artery disease)	NA	9.0 (2016/18)
Eberly et al. [47]	US	594 058	ASCVD (coronary artery, cerebrovascular, or peripheral artery disease)	3.0 (2015)	9.8 (2019)
Nargesi et al. [22]	US (NHANES)	264	ASCVD (previous history of event)	NA	7.4 (2017/18)
Mahtta et al. [49]	US	537,980	Established ASCVD (no detailed definition)	NA	11.2 (2020)
Devineni et al. [51]	US	31,394	Established ASCVD (no detailed definition)	NA	8.6 (2018/22)
Hao et al. [53]	Canada	680	ASCVD (events or endovascular procedures)	NA	17.3 (2018/19)
Ozaki et al. [52]	Ontario, Canada	132 196	ASCVD (events or revascularization)	7.0 (2016/17)	20.1 (2019/20)
Bidulka et al. [58]	England	8466	ASCVD (composite of ischaemic heart disease, unstable angina, previous myocardial infarction, previous stroke or HF)	11.0 (2015/16)	28.0 (2019/20)
Nanna et al. [59]	US	194 264 (2018) 85 956 (2021)	ASCVD (coronary artery disease, peripheral arterial disease, or atherosclerotic cerebrovascular disease)	5.8 (2018)	12.9 (2021)
Barth et al. [60]	Germany	16,006	ASCVD (events or revascularization)	13.9 (2017−18)	20.4 (2019−20)
Heart failure (HF)					
Eberly et al. [47]	US	26 054	HFrEF	1.9 (2015)	7.6 (2019)
Nargesi et al. [22]	US (NHANES)	100	HF (any type)	NA	9.0 (2017/18)
Pierce et al. [57]	USA	21 830	HFrEF (hospitalization)	NA	26.2 (2021/22)
Stolfo et al. [61]	Sweden	8192	HFrEF	46.2 (2020)	69.8 (2022)
ASCVD or HF					
Dave et al. [46]	US	90 096	ASCVD (myocardial infarction/stroke) or HF (any type)	8.8 (2013)	12.2 (2018)
Hussain et al. [50]	US	105,799	ASCVD (established) or HF (any type)	NA	14.6 (2020)
Chronic kidney disease (CKD)					
Eberly et al. [47]	US	92 485	CKD (stages 1−3)	2.1 (2015)	7.5 (2019)
Nargesi et al. [22]	US (NHANES)	408	CKD (eGFR G3 or UACR A2-A3)	NA	6.0 (2017/18)
Harris et al. [56]	USA	33 891	CKD (eGFR 15−60 ml/min per 1.73 m^2)	4.0 (2015)	8.0 (2019) 13.0 (2020 Q1)
Jeong et al. [48]	Korea	905	CKD (eGFR G1-G5 and UACR A1-A3)	NA	32.9 (2019/20)
Zhuo et al. [55]	USA	22 653	CKD (G 3−5)	NA	6.0 (2021)
Lau et al. [54]	Alberta health	76 630	CKD eGFR < 90 with proteinuria or eGFR < 60 or high UACR	NA	7.1 (2019)
Nicholas et al. [62]	USA	39 158	eGFR < 60 or high UACR ≥ 30 mg/g	NA	6.0 (2019/20)
Seetharaman et al. [63]	India	253	CKD (G 1−4)	NA	3.1 (NA)

eGFR: estimated glomerular filtration rate. HFrEF: heart failure with reduced ejection fraction. NA: not available. UACR: urinary albumin/creatinine ratio.

and 5 August 2022 (of note, this date coincided with the approval of SGLT2i for the treatment of HFrEF in Sweden) [61].

Surprisingly, several studies reported lower rates of SGLT2i use in T2DM patients with comorbidities (ASCVD, HF, CKD) compared with those without comorbidities. In a study carried out in England, when stratifying by prevalent ASCVD status, it has been reported that lower predicted percentages of people with prevalent ASCVD prescribed SGLT2is compared with people without prevalent ASCVD, a difference found across all ethnicity groups and all levels of social deprivation [58]. According to another observational study using linked population-based health data in Ontario, only 20 % of patients with T2DM and ASCVD were prescribed SGLT2is in 2019/20, but history of HF and kidney disease, were shown to be independent factors of lower SGLT2i prescribing [52]. Data from the "Northern Alberta Primary Care Research Network" in Canada showed that SGLT2is were less likely to be prescribed to patients with pre-existing ASCVD, HF, and/or CKD: surprisingly, the use of SGLT2is in these patients was lower than in patients without cardiorenal comorbidities (14.9 % vs 21.2 %; $P < 0.05$) [53]. Similarly, in a retrospective US analysis, T2DM patients with HF were less likely to start SGLT2is rather than DPP-4is compared with patients without these conditions (RRR 0.83, 95 % CI 0.80−0.87) [24]. In a recent survey in a German real-world setting, SGLT2i use slightly increased between 2027/18 and 2019/20, with no major difference among patients with ASCVD (from 13.9 to 20.4 %) and among patients with T2DM and without ASCVD (from 12.1 % to 16.6 %) [60]. However, in the already mentioned multinational DISCOVERY survey, coronary artery disease was associated with an almost 30 % increased use of SGLT2is (or GLP-1RAs) compared with patients without ASCVD [64]. Overall, most observations were clearly in contradiction with the international guidelines [17–20] that emphasized the benefit from this pharmacological class in both placebo-controlled RCTs and real-life studies versus active comparators.

Another intriguing finding was the huge variation in the use of SGLT2is across different patient groups or country areas. Among 537,980 patients with ASCVD and T2DM across 130 Veterans facilities, only 11.2 % of patients received an SGLT2i, with high residual facility-level variation in the use of these drugs [49]. This was confirmed in another similar study among 105,799 T2DM patients with ASCVD or HF: only 14.6 % received SGLT2is, with again a high (55 %) residual variation in SGLT2i use among similar patients across Veterans Affairs facilities [50]. In a cross-sectional study conducted between 2014 and 2019 in 50 US states and the District of Columbia, SGLT2i therapy increased in use during the study period, yet with a considerable variation among states in their relative use [65]. In DISCOVER, a global, prospective, observational survey among 14,576 patients with T2DM from 37 countries, substantial country-level variability exists independent of patient demographic and clinical factors, suggesting structural barriers may limit more widespread use of these medications with CV and renal protection properties [64].

Addressing the paradox and bridging the gap

Several factors or patient characteristics appeared to influence the rate of use of SGLT2is. Of note, racial, ethnic, and socioeconomic inequities in SGLT2i use were noticed among patients with T2DM as recently reviewed [66]. These inequities were noticed in different countries, in the US [47,51], in Canada [52] and in England [58]. In a Canadian study, age 75 years or older, female sex, and low income were shown to be independent factors of lower SGLT2i prescribing [52]. In "NIH Precision Medicine Initiative All of Us Research Program", only 8.6 % of patients with T2DM and ASCVD were treated with an SGLT2i and SGLT2i use was < 10 % in those with HF, and their use was even lower among underserved groups [51]. Even when a universal healthcare system is developed as in Denmark, a low socioeconomic position was consistently associated with a lower probability of initiating an SGLT2i in patients with T2DM despite they were eligible for such protective therapy [67]. Another study reported that among patients with diabetes, advanced CKD stages were associated with lower odds of SGLT2i prescription, whereas at least one subspecialist visit in the previous year was associated with higher odds of SGLT2i prescription [55]. According to the data from the nationwide Veterans Affairs health care system, patients receiving SGLT2is were younger men with higher hemoglobin A1c and eGFR and were more likely to have HFrEF and ischaemic heart disease [50].

Addressing the paradox of an underuse in clinical practice of SGLT2is with evidence-proven CV and renal protective properties should help reduce the increased morbidity and mortality in this T2DM population with ASCVD, HF and/or CKD [15,24,68]. The implementation of clinician and patient dedicated education should encourage uptake of these drugs in clinical practice, potentially improving long-term health outcomes among patients with T2DM at high CV and renal risk [69]. An original RCT demonstrated that a coordinated, multifaceted intervention increased the prescription of evidence-based therapies in adults with T2DM and ASCVD, including the use of SGLT2is [70]. As recently reviewed [26], three key-strategies should be implemented to reduce the underuse of SGLT2is in daily clinical practice: (i) avoiding medical delayed initiation (therapeutic inertia) or inappropriate discontinuation (including during hospital stay) [71]; (ii) improving patient drug adherence and persistence; and (iii) promoting an easier access to SGLT2is inside the health care system. A recent comparative population-based retrospective cohort study using primary care data from the UK Clinical Practice Research Datalink revealed that the rate (60 %) of treatment discontinuation among SGLT2i users was significantly higher for those with low eGFR and minimal contact with the healthcare system, whereas efficacy endpoints, such as HF and glycated hemoglobin level, were not associated with treatment discontinuation [72]. Another study that evaluated the cost effectiveness of SGLT2i therapy in a routine care T2DM population that meets Dutch reimbursement criteria concluded that SGLT2i are likely to be cost effective when compared with usual care although the Dutch reimbursement indications led to a target group that deviates from trial populations [73].

Because of the complexity of the problem, multifaceted and coordinated interventions involving not only clinicians and patients, but also professional societies (responsible for promoting guidelines), payers, pharmaceutical companies and health care systems in general must be implemented to favor the adoption of these medications as part of routine CV care (and renal protection as well) among patients with T2DM [74,75].

Conclusion

Over the last decade, SGLT2is have changed the treatment paradigm for patients with T2DM, especially those with or at high risk of ASCVD, HF or CKD, after the demonstration of a cardiovascular and renal protection in large placebo-controlled clinical trials, a clinical benefit confirmed in many observational studies worldwide. These medications are now recommended in international guidelines beyond their effects on glucose control and have become a powerful resource for health care providers in patients with T2DM and highly prevalent comorbidities. However, SGLT2is remain vastly underused in clinical practice despite their broad cardiorenal benefits. A compilation of real-world studies showed that only a minority of patients were treated with SGLT2is, yet a trend of an increase was systematically reported in recent years. Nevertheless, an astonishing finding was the report in several real-life studies that SGLT2is were less frequently used in T2DM patients with ASCVD, HF or even more CKD than in people without these complications, despite most patients should benefit. Multifaceted coordinated interventions are most probably needed to overcome barriers to the implementation of evidence-based therapies with CV and renal benefits and facilitate their optimal use in the population with T2DM.

Funding details

No sources of funding were used to assist in the preparation of this manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The author has received lecturer/scientific advisor/clinical investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, NovoNordisk and Sanofi. He worked as clinical investigator in TECOS, EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58, LEADER and HARMONY Outcomes cardiovascular outcome trials.

References

[1] Ahmad E, Lim S, Lamptey R, et al. Type 2 diabetes. Lancet 2022;400(10365):1803–20.
[2] Braunwald E. Gliflozins in the management of cardiovascular disease. N Engl J Med 2022;386(21):2024–34.
[3] Pandey A, Khan MS, Patel KV, et al. Predicting and preventing heart failure in type 2 diabetes. Lancet Diabetes Endocrinol 2023;11(8):607–24.
[4] Muskiet MHA, Wheeler DC, Heerspink HJL. New pharmacological strategies for protecting kidney function in type 2 diabetes. Lancet Diabetes Endocrinol 2019;7(5):397–412.
[5] Scheen AJ. Sodium-glucose co-transporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Rev Endocrinol 2020;16(10):556–77.
[6] Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editors' expert forum. Diabetes Care 2018;41(1):14–31.
[7] Ghosh-Swaby OR, Goodman SG, Leiter LA, et al. Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials. Lancet Diabetes Endocrinol 2020;8(5):418–35.
[8] Wright AK, Carr MJ, Kontopantelis E, et al. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. Diabetes Care 2022;45(4):909–18.
[9] Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet 2022;400(10354):757–67.
[10] Scheen AJ. Clinical pharmacology of antidiabetic drugs: what can be expected of their use? Presse Med 2022;52(1):104158.
[11] Marx N, Muller-Wieland D. SGLT2 inhibitors in heart failure and type 2 diabetes: from efficacy in trials towards effectiveness in the real world. Eur Heart J 2023;44(24):2231–3.
[12] Scheen AJ. The current role of SGLT2 inhibitors in type 2 diabetes and beyond: a narrative review. Expert Rev Endocrinol Metab 2023;18(4):271–82.
[13] Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7(11):845–54.
[14] Nuffield Department of Population Health Renal Studies G, Consortium SiM-AC-RT. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet 2022;400(10365):1788–801.
[15] Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76(9):1117–45.
[16] Brown E, Heerspink HJL, Cuthbertson DJ, et al. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet 2021;398(10296):262–76.
[17] Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2022;65(12):1925–66.
[18] Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: comprehensive type 2 diabetes management algorithm - 2023 update. Endocr Pract 2023;29(5):305–40.
[19] Marx N, Federici M, Schütt K, et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023. doi: 10.1093/eurheartj/ehad192.
[20] Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102(5S):S1–S127.
[21] Lim CE, Pasternak B, Eliasson B, et al. Use of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists according to the 2019 ESC guidelines and the 2019 ADA/EASD consensus report in a national population of patients with type 2 diabetes. Eur J Prev Cardiol 2023;30(8):634–43.
[22] Nargesi AA, Jeyashanmugaraja GP, Desai N, et al. Contemporary national patterns of eligibility and use of novel cardioprotective antihyperglycemic agents in type 2 diabetes mellitus. J Am Heart Assoc 2021;10(13):e021084.
[23] Abrahami D, D'Andrea E, Yin H, et al. Contemporary trends in the utilization of second-line pharmacological therapies for type 2 diabetes in the United States and the United Kingdom. Diabetes Obes Metab 2023;25(10):2980–8.
[24] McCoy RG, Van Houten HK, Karaca-Mandic P, et al. Second-line therapy for type 2 diabetes management: the treatment/benefit paradox of cardiovascular and kidney comorbidities. Diabetes Care 2021;44(10):2302–11.
[25] Lim LL, Chow E, Chan JCN. Cardiorenal diseases in type 2 diabetes mellitus: clinical trials and real-world practice. Nat Rev Endocrinol 2023;19(3):151–63.
[26] Scheen AJ. Bridging the gap in cardiovascular care in diabetic patients: are cardioprotective antihyperglycemic agents underutilized? Exp Rev Clin Pharmacol 2023 in press.
[27] Giugliano D, Longo M, Signoriello S, et al. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. Cardiovasc Diabetol 2022;21(1):42.
[28] Zheng C, Lin M, Chen Y, et al. Effects of sodium-glucose cotransporter type 2 inhibitors on cardiovascular, renal, and safety outcomes in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. Cardiovasc Diabetol 2021;20(1):83.
[29] Rahman H, Khan SU, Lone AN, et al. Sodium-glucose cotransporter-2 inhibitors and primary prevention of atherosclerotic cardiovascular disease: a meta-analysis of randomized trials and systematic review. J Am Heart Assoc 2023;12(16):e030578.
[30] Lin DS, Yu AL, Lo HY, et al. Differential effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular and renal outcomes according to renal function: a dose-response meta-analysis involving 10 randomized clinical trials and 71 553 individuals. Eur J Endocrinol 2023;189(1):S17–25.
[31] Gager GM, Gelbenegger G, Jilma B, et al. Cardiovascular outcome in patients treated with SGLT2 inhibitors for heart failure: a meta-analysis. Front Cardiovasc Med 2021;8:691907.
[32] Xiang B, Zhang R, Wu X, et al. Optimal pharmacologic treatment of heart failure with preserved and mildly reduced ejection fraction: a meta-analysis. JAMA Netw Open 2022;5(9):e2231963.
[33] Marilly E, Cottin J, Cabrera N, et al. SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials balancing their risks and benefits. Diabetologia 2022;65(12):2000–10.
[34] Scheen AJ. SGLT2 inhibitors: benefit/risk balance. Curr Diabetes Rep 2016;16(10):92.
[35] Scheen AJ. Cardiovascular and renal outcomes with SGLT2 inhibitors: real-life observational studies in older patients with type 2 diabetes. Diabetes Epidemiol Manag 2023;10:100135.
[36] Li CX, Liang S, Gao L, et al. Cardiovascular outcomes associated with SGLT-2 inhibitors versus other glucose-lowering drugs in patients with type 2 diabetes: a real-world systematic review and meta-analysis. PLoS ONE 2021;16(2):e0244689.
[37] Mascolo A, Scavone C, Scisciola L, et al. SGLT-2 inhibitors reduce the risk of cerebrovascular/cardiovascular outcomes and mortality: a systematic review and meta-analysis of retrospective cohort studies. Pharmacol Res 2021;172:105836.
[38] Singh AK, Singh R. Heart failure hospitalization with SGLT-2 inhibitors: a systematic review and meta-analysis of randomized controlled and observational studies. Expert Rev Clin Pharmacol 2019;12(4):299–308.
[39] Hinton W, Ansari AS, Whyte MB, et al. Sodium-glucose co-transporter-2 inhibitors in type 2 diabetes: are clinical trial benefits for heart failure reflected in real-world clinical practice? A systematic review and meta-analysis of observational studies. Diabetes Obes Metab 2023;25(2):501–15.
[40] Forbes AK, Suckling RJ, Hinton W, et al. Sodium-glucose cotransporter-2 inhibitors and kidney outcomes in real-world type 2 diabetes populations: a systematic review and meta-analysis of observational studies. Diabetes Obes Metab 2023;25(8):2310–30.
[41] Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. Curr Diabetes Rep 2022;22(1):39–52.
[42] Fadini GP, Del Prato S, Avogaro A, et al. Challenges and opportunities in real-world evidence on the renal effects of sodium-glucose cotransporter-2 inhibitors. Diabetes Obes Metab 2022;24(2):177–86.
[43] Evans M, Morgan AR, Whyte MB, et al. New therapeutic horizons in chronic kidney disease: the role of SGLT2 inhibitors in clinical practice. Drugs 2022;82(2):97–108.
[44] Nishi L, Ghossein C, Srivastava A. Increasing sodium-glucose cotransporter 2 inhibitor use in CKD: perspectives and presentation of a clinical pathway. Kidney Med 2022;4(5):100446.
[45] Arnold SV, de Lemos JA, Rosenson RS, et al. Use of guideline-recommended risk reduction strategies among patients with diabetes and atherosclerotic cardiovascular disease. Circulation 2019;140(7):618–20.
[46] Dave CV, Schneeweiss S, Wexler DJ, et al. Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013-2018. Diabetes Care 2020;43(4):921–4.
[47] Eberly LA, Yang L, Eneanya ND, et al. Association of race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US. JAMA Netw Open 2021;4(4):e216139.
[48] Jeong SJ, Lee SE, Shin DH, et al. Barriers to initiating SGLT2 inhibitors in diabetic kidney disease: a real-world study. BMC Nephrol 2021;22(1):177.
[49] Mahtta D, Ramsey DJ, Lee MT, et al. Utilization rates of SGLT2 inhibitors and GLP-1 receptor agonists and their facility-level variation among patients with

atherosclerotic cardiovascular disease and type 2 diabetes: insights from the department of Veterans Affairs. Diabetes Care 2022;45(2):372–80.
[50] Hussain A, Ramsey D, Lee M, et al. Utilization rates of SGLT2 inhibitors among patients with type 2 diabetes, heart failure, and atherosclerotic cardiovascular disease: insights from the Department of Veterans Affairs. JACC Heart Fail 2023;11(8 Pt 1):933–42.
[51] Devineni D, Akbarpour M, Gong Y, et al. Inadequate use of newer treatments and glycemic control by cardiovascular risk and sociodemographic groups in US adults with diabetes in the NIH Precision Medicine Initiative All of Us Research Program. Cardiovasc Drugs Ther 2022 Nov 15. doi: 10.1007/s10557-022-07403-2.
[52] Ozaki AF, Ko DT, Chong A, et al. Prescribing patterns and factors associated with sodium-glucose cotransporter-2 inhibitor prescribing in patients with diabetes mellitus and atherosclerotic cardiovascular disease. CMAJ Open 2023;11(3):E494–503.
[53] Hao R, Myroniuk T, McGuckin T, et al. Underuse of cardiorenal protective agents in high-risk diabetes patients in primary care: a cross-sectional study. BMC Prim Care 2022;23(1):124.
[54] Lau D, Pannu N, Yeung RO, et al. Use of sodium-glucose cotransporter 2 inhibitors in Alberta adults with chronic kidney disease: a cross-sectional study identifying care gaps to inform knowledge translation. CMAJ Open 2023;11(1):E101–E09.
[55] Zhuo M, Li J, Buckley LF, et al. Prescribing patterns of sodium-glucose cotransporter-2 inhibitors in patients with CKD: a cross-sectional registry analysis. Kidney360 2022;3(3):455–64.
[56] Harris ST, Patorno E, Zhuo M, et al. Prescribing trends of antidiabetes medications in patients with type 2 diabetes and diabetic kidney disease, a cohort study. Diabetes Care 2021;44(10):2293–301.
[57] Pierce JB, Vaduganathan M, Fonarow GC, et al. Contemporary use of sodium-glucose cotransporter-2 inhibitor therapy among patients hospitalized for heart failure with reduced ejection fraction in the US: the get with the guidelines-heart failure registry. JAMA Cardiol 2023;8(7):652–61.
[58] Bidulka P, Mathur R, Lugo-Palacios DG, et al. Ethnic and socioeconomic disparities in initiation of second-line antidiabetic treatment for people with type 2 diabetes in England: a cross-sectional study. Diabetes Obes Metab 2023;25(1):282–92.
[59] Nanna MG, Kolkailah AA, Page C, et al. Use of sodium-glucose cotransporter 2 inhibitors and glucagonlike peptide-1 receptor agonists in patients with diabetes and cardiovascular disease in community practice. JAMA Cardiol 2023;8(1):89–95.
[60] Barth SD, Kostev K, Krensel M, et al. Do glucagonlike peptide-1 receptor agonist and sodium-glucose co-transporter 2 inhibitor prescriptions in Germany reflect recommendations for type 2 diabetes with cardiovascular disease of the ADA/EASD consensus report? Exp Clin Endocrinol Diabetes 2023;131(3):153–61.
[61] Stolfo D, Lund LH, Benson L, et al. Real-world use of sodium-glucose cotransporter 2 inhibitors in patients with heart failure and reduced ejection fraction: data from the Swedish Heart Failure Registry. Eur J Heart Fail 2023;25:1648–58.
[62] Nicholas SB, Daratha KB, Alicic RZ, et al. Prescription of guideline-directed medical therapies in patients with diabetes and chronic kidney disease from the CURE-CKD Registry, 2019-2020. Diabetes Obes Metab 2023;25(10):2970–9.
[63] Seetharaman R, Advani M, Mali S, et al. A drug utilisation pattern in non-dialysis patients of diabetic nephropathy in a government-run tertiary care hospital in South-Asia. J Basic Clin Physiol Pharmacol 2023;34(3):371–81.
[64] Arnold SV, Tang F, Cooper A, et al. Global use of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. Results from DISCOVER. BMC Endocr Disord 2022;22(1):111.
[65] Zhai MZ, Avorn J, Liu J, et al. Variations in use of diabetes drugs with cardiovascular benefits among medicaid patients. JAMA Netw Open 2022;5(11):e2240117.
[66] Karagiannis T, Bekiari E, Tsapas A. Socioeconomic aspects of incretin-based therapy. Diabetologia 2023;66(10):1859–68.
[67] Falkentoft AC, Andersen J, Malik ME, et al. Impact of socioeconomic position on initiation of SGLT-2 inhibitors or GLP-1 receptor agonists in patients with type 2 diabetes - a Danish nationwide observational study. Lancet Reg Health Eur 2022;14:100308.
[68] Yau K, Dharia A, Alrowiyti I, et al. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. Kidney Int Rep 2022;7(7):1463–76.
[69] Khunti K, Jabbour S, Cos X, et al. Sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes: barriers and solutions for improving uptake in routine clinical practice. Diabetes Obes Metab 2022;24(7):1187–96.
[70] Pagidipati NJ, Nelson AJ, Kaltenbach LA, et al. Coordinated care to optimize cardiovascular preventive therapies in type 2 diabetes: a randomized clinical trial. JAMA 2023;329(15):1261–70.
[71] Scheen AJ. Underuse of glucose-lowering medications associated with cardiorenal protection in type 2 diabetes: from delayed initiation to untimely discontinuation. Lancet Reg Health Eur 2023;29:100627.
[72] Alkabbani W, Shah BR, Zongo A, et al. Post-initiation predictors of discontinuation of the sodium-glucose cotransporter-2 inhibitors: a comparative cohort study from the United Kingdom. Diabetes Obes Metab 2023 Aug 10. doi: 10.1111/dom.15241.
[73] Li X, Hoogenveen R, El Alili M, et al. Cost-effectiveness of SGLT2 inhibitors in a real-world population: a MICADO model-based analysis using routine aata from a GP registry. Pharmacoeconomics 2023;41(10):1249–62.
[74] Nelson AJ, Pagidipati NJ, Aroda VR, et al. Incorporating SGLT2i and GLP-1RA for cardiovascular and kidney disease risk reduction: call for action to the cardiology community. Circulation 2021;144(1):74–84.
[75] Dievart F, Darmon P, Halimi JM, et al. Quand et comment utiliser les inhibiteurs de la SGLT2 ou gliflozines en pratique clinique ? Un consensus proposé par la Société francophone du diabète (SFD), la Société française de cardiologie (SFC), le Collège national des cardiologues français (CNCF) et la Société francophone de néphrologie, dialyse et transplantation (SFNDT). Nephrol Ther 2023;19(4):251–77.