



REVIEW

Beyond the Glycaemic Control of Dapagliflozin: Microangiopathy and Non-classical Complications

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Received: December 6, 2021 / Accepted: February 21, 2022 / Published online: March 25, 2022
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ABSTRACT

Dapagliflozin is a selective sodium-glucose cotransporter 2 inhibitor (SGLT2i) indicated for the treatment of type 2 diabetes mellitus (T2DM), heart failure (HF) with reduced ejection fraction (EF) and chronic kidney disease (CKD). In monotherapy or as an additive therapy, dapagliflozin aids glycaemic control, is associated with reductions in blood pressure and weight, and promotes a favourable lipid profile. In this review, we address the impact of dapagliflozin on cardiovascular risk factors and common microangiopathic complications such as kidney disease and retinopathy in patients

with T2DM. Furthermore, we evaluate its potential beneficial effects on other less frequent complications of diabetes, such as macular oedema, cognitive impairment, non-alcoholic fatty liver disease and respiratory disorders during sleep. Moreover, the underuse of SGLT2i in clinical practice is discussed. Our goal is to help translate this evidence into clinical practice.

Keywords: Dapagliflozin; Sodium-glucose cotransporter 2 inhibitors; Diabetes mellitus; Cardiometabolic risk factors; Therapeutic inertia; Diabetic angiopathy

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Key Summary Points

Dapagliflozin is a selective sodium-glucose cotransporter 2 inhibitor (SGLT2i) indicated for the treatment of type 2 diabetes mellitus (T2DM), heart failure with reduced ejection fraction and chronic kidney disease.

Dapagliflozin may also contribute to the control of cardiovascular risk factors (excess body weight, blood pressure and dyslipidaemia), the prevention of microvascular complications (nephropathy and retinopathy), and other non-classical complications of T2DM such as macular oedema, cognitive impairment, non-alcoholic fatty liver disease and sleep breathing disorders.

There is an underuse of SGLT2i in general and dapagliflozin in particular, even in patients whose profiles suggest they could greatly benefit from SGLT2i treatment, indicating that greater effort is needed to translate scientific evidence into actual clinical practice.

INTRODUCTION

Dapagliflozin is a highly selective and reversible inhibitor of the sodium glucose cotransporter type 2 (SGLT2) [1, 2]. Its inhibitory effect on SGLT2 reduces glucose reabsorption in the renal proximal tubule, leading to a concomitant decrease in sodium reabsorption, increased urinary glucose excretion and osmotic diuresis [3].

Dapagliflozin is indicated in adults for the treatment of inadequately controlled type 2 diabetes mellitus (T2DM) in combination with diet and exercise. It is used as monotherapy when metformin is not deemed appropriate or in addition to other drugs for the treatment of T2DM [3]. Additionally, indications for dapagliflozin have been recently approved in adults for the treatment of symptomatic chronic heart

failure (HF) with reduced ejection fraction (EF) [3] and chronic kidney disease (CKD), with a glomerular filtration rate (GFR) ≥ 25 ml/min/1.73 m² established as the limit for starting treatment in all indications.

There is increasing evidence, based on both clinical trials and real-life studies, that dapagliflozin is also associated with greater body weight reduction and better blood pressure (BP) control compared to placebo in a wide range of patients [1]. Furthermore, dapagliflozin has been associated with both cardiovascular (CV) and renal benefits along with a good safety profile, including a low risk of hypoglycaemia [1]. Its use may also be beneficial in the prevention of microvascular complications such as renal disease or retinopathy in patients with T2DM [4–10].

This article reviews the effects of dapagliflozin on different CV risk factors and microvascular complications (renal disease and retinopathy) of T2DM, and it explores the impact of dapagliflozin on non-classical complications of diabetes, such as macular oedema, cognitive impairment, non-alcoholic fatty liver disease and respiratory disorders during sleep. Finally, we provide data on the mismatch between the wide range of patients with T2DM who could benefit from the use of SGLT2 inhibitors (SGLT2i) and real-life prescription rates, with the aim of translating the benefit shown by the evidence into clinical practice [11].

METHODS

Literature Search

PubMed was searched for “dapagliflozin” or “diabetes therapy” or “SGLT2i” or “selective sodium and glucose 2 transporter” and “blood pressure” or “hypertension” or “lipid profile” or “dyslipidemia” or “diabetic nephropathy” or “chronic kidney disease” or “diabetic retinopathy” or “macular edema” or “non-alcoholic fatty liver disease” or “cognitive impairment” or “Alzheimer’s disease” or “sleep breathing disorders” or “syndrome obstructive sleep apnea/hypopnea”. In addition, the terms “therapeutic

inertia” or “prescription pattern” or “real-world use” or “prescription” were also included.

Articles published in English until 1 June 2021 were selected. The relevance of the abstracts was assessed and then full texts were obtained. The reference lists of the selected articles were also reviewed to identify additional studies relevant to our review.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Impact of Dapagliflozin on Cardiovascular Risk Factors

High Blood Pressure (HBP)

Hypertension (HT) and T2DM have an additive effect that is associated with increased arterial stiffness and consequently an increased CV risk [12]. Dapagliflozin induces a modest reduction in BP in patients with T2DM, along with a risk of orthostatic reactions similar to that associated with placebo [13, 14]. This benefit has been observed in large randomised placebo-controlled trials such as DECLARE-TIMI 58 and DAPA-HF, as well as in patient cohorts and real-life studies [13, 15–19].

This decrease in BP associated with dapagliflozin appears to be largely explained by intravascular volume depletion, due to its diuretic and natriuretic properties [1]. However, a direct vasodilatory effect on the efferent arteriole, modulation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, as well as increased urinary excretion of uric acid have also been suggested [4, 20]. Importantly, the decrease in BP is independent of the estimated glomerular filtration rate [21].

An aggregate analysis of 13 clinical trials, including 2360 patients with T2DM treated with dapagliflozin 10 mg/day and 2295 patients with T2DM treated with placebo, showed that

the greatest decrease in BP with dapagliflozin occurred in participants with baseline HT [13]. Thus, the mean adjusted decrease in systolic BP (SBP) and diastolic BP (DBP) from baseline to week 24 (subtracting the placebo effect) was – 3.6 mmHg and – 1.2 mmHg, respectively, for patients with baseline HT (SBP \geq 140 mmHg). In non-hypertensive patients, the decrease in SBP and DBP was – 2.6 mmHg and – 1.2 mmHg, respectively. The proportion of patients experiencing orthostatic hypotension was similar in both groups and there was no clinically relevant difference between dapagliflozin and placebo in heart rate [13].

It is interesting to note that the effects of dapagliflozin on BP are evident as early as the first week after treatment initiation, and are maintained after 4 years of follow-up [13, 22].

Dyslipidaemia

SGLT2i are involved in the regulation of key molecules for lipid synthesis and transport, as well as fatty acid oxidation, promoting favourable changes in lipid metabolism [23]. Most studies suggest that treatment with SGLT2i produces small reductions in triglyceride (TG) levels and slight elevations in total cholesterol and high-density lipoprotein cholesterol (HDL-C) [24–29]; however, there are a few studies that have not observed these changes [30].

With regard to low-density lipoprotein cholesterol (LDL-C), both a decrease and an increase in LDL-C associated with dapagliflozin treatment have been reported [24, 28, 29]. This contradiction could be explained by the different effects of the SGLT2i on different LDL-C fractions [31]. Dapagliflozin is associated with an elevation of large, buoyant LDL particles (lb-LDL) and a decrease in small, dense LDL particles (sd LDLc), favouring the development of a less atherogenic lipid profile [31]. Decreases in several indices associated with CV disease, such as the plasma atherogenic index [$\log(\text{TG}/\text{HDL-C})$] or the triglyceride-glucose (TyG) index, have also been reported in patients treated with dapagliflozin [32].

Dapagliflozin and Classical Microangiopathic Complications

Diabetic Nephropathy

Patients with T2DM have a high residual risk of developing renal complications despite intensive glycaemic control, the use of renin–angiotensin–aldosterone system inhibitors, and BP and lipid control [4, 33]. However, the emergence of SGLT2i has led to the discovery of new mechanisms of nephroprotection, both renal and extrarenal [4, 19] (Fig. 1).

At the renal level, SGLT2i promote diuresis and natriuresis. Reduced sodium reabsorption in the proximal convoluted tubule increases sodium influx into the macula densa. This process activates tubuloglomerular feedback, which ultimately leads to correction of vasodilation of the afferent arteriole and, as a consequence, to a decrease in intraglomerular pressure and diabetes-related hyperfiltration. In addition, sodium chloride delivery to the distal nephron reduces the GFR by increasing the hydrostatic pressure in Bowman’s space [4, 19]. Furthermore, the use of SGLT2i is associated with a reduction in biomarkers of inflammation and fibrosis in tubular cells and a reduction in their oxygen demand, enhancing the protective effect on tubular cells. They also induce an increase in erythropoietin production and an

increase in haematocrit [19]. All these changes result in the long-term preservation of the eGFR.

At the extrarenal level, SGLT2i are associated with a reduction in BP, not only because of the osmotic diuresis they produce, but also because they induce a direct vasodilatory effect [4, 5]. In addition, they modulate the renin–angiotensin–aldosterone system as well as the sympathetic nervous system, possibly contributing to a reduction in arterial stiffness. Moreover, they promote a negative sodium balance, preferentially mobilising sodium from the interstitial compartment. Through this mechanism, they preserve the effective circulating volume and support renal haemodynamics. Similarly, SGLT2i reduce reabsorption and promote uric acid excretion, which may contribute to a reduced risk of renal impairment. Finally, there is also evidence to suggest that dapagliflozin attenuates glucotoxicity and lipotoxicity, which may help prevent renal fibrosis [4, 5, 19].

In the DECLARE-TIMI 58 study, where the median baseline estimated GFR was 85.2 ml/min/1.73 m², a renal composite event ($\leq 40\%$ decrease in estimated GFR, end-stage renal disease, or renal or CV death) occurred in 4.3% of the dapagliflozin group and 5.6% of the placebo group (HR: 0.76, 95% confidence interval:

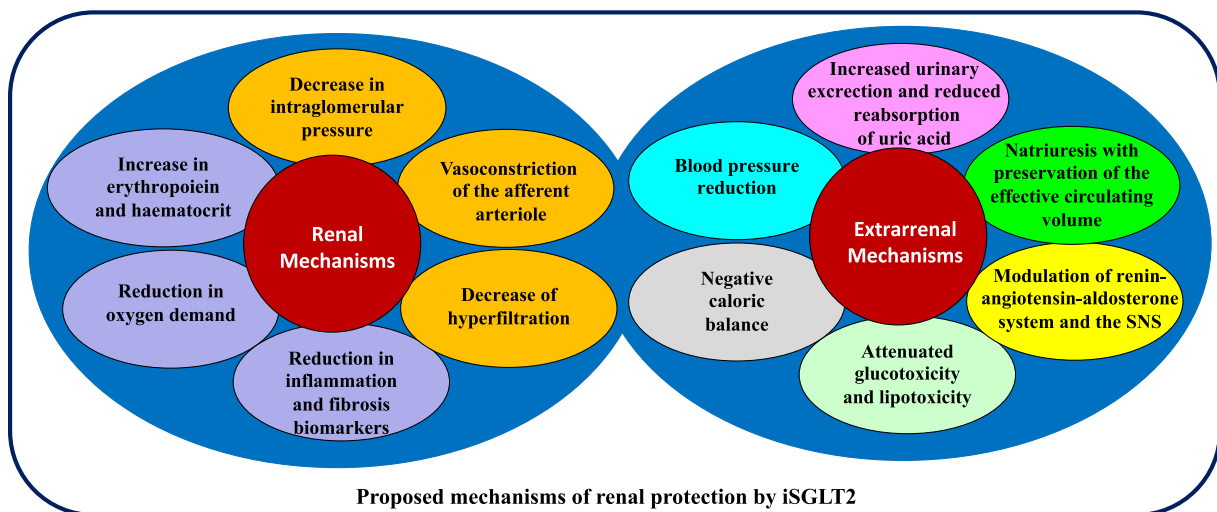


Fig. 1 Proposed renal and extrarenal mechanism of renal protection by iSGLT2

Table 1 Main baseline features of participants in the DAPA-CKD study

<i>n</i>	4304
Intervention	Dapagliflozin 10 mg/day vs placebo
Main inclusion criteria	Adults with or without T2DM; eGFR: 25–75 ml/min/1.73 m ² ; UACR: 200–5000 mg/g
Age (years)	61.8 ± 12.1
Males	2852 (66.3)
Caucasians	2290 (53.2)
Participants with T2DM	2906 (67.5)
eGFR (ml/min/1.72 m ²)	43.1 ± 12.4
Median UACR (mg/g)	949
Cardiovascular disease	1610 (37.4)
Prior medication	
ACEi	1354 (31.4)
ARA2	2870 (66.6)
Diuretics	1882 (43.7)
Statin	2758 (64.0)
Follow-up median (years)	2.4

Data are expressed as the median, mean ± standard deviation, or total number (percentage); *UACR* urinary albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate, *ARBs* angiotensin receptor blockers, *T2DM* type 2 diabetes mellitus, *ACEi* angiotensin-converting enzyme inhibitors, *ARA2* aldosterone receptor antagonists type 2

0.67–0.87) within the median follow-up of 4.2 years [15]. The benefit was independent of the baseline GFR or the presence or absence of CVD [34]. The DAPA-CKD study included 4,304 subjects with and without T2DM who had an estimated GFR of 25–75 ml/min/1.73 m² and an albumin/creatinine ratio between 200 and 5000 mg/g and were randomised to

dapagliflozin 10 mg/day or placebo [35]. The baseline characteristics of the study population are shown in Table 1. After 2.4 years of follow-up, the primary composite endpoint (a sustained decrease in eGFR of at least 50%, end-stage renal disease, or death from renal or CV causes) had occurred in 9.2% of participants in the dapagliflozin group and 14.5% in the placebo group (HR: 0.61, 95% CI 0.51–0.72, *p* < 0.001). Dapagliflozin also decreased the secondary endpoints of renal events, HF hospitalisation/CV death and all-cause death (Table 2) [34].

It is also worth noting the association between dapagliflozin and a decrease in the progression of albuminuria, attributed to both a decrease in glomerular pressure and an improvement in the albumin reabsorption capacity of tubular cells [36]. This favourable effect appears to be independent of the estimated GFR and basal albumin/creatinine ratio and to be present in patients with and without T2DM [36, 39]. Several meta-analyses of clinical trials with SGLT2i [38, 39] and real-life studies with large cohorts [40, 41] allow for the generalization of the renal results of clinical trials to routine clinical practice [38–41].

Diabetic Retinopathy

Diabetic retinopathy (DR) is a diabetes-specific complication that occurs in more than one-third of patients and accounts for 80% of cases of total vision loss in the diabetic population [42]. Paradoxically, an excessively rapid fall in blood glucose is a risk factor for the onset and progression of DR. The highest risk is associated with the use of insulin or sulphonylureas, whereas SGLT2i are considered safe in this respect [42]. In a meta-analysis of 37 clinical trials that looked at the risk of DR with different hypoglycaemic agents in 100,928 patients with T2DM, SGLT2i were not associated with an increased risk of DR compared to placebo [43]. Furthermore, in vitro evidence suggests that SGLT2i may have a protective role for the retina [44]. This benefit would be mediated, beyond their influence on classical CV risk factors, by a protective role at the level of the blood-retinal barrier and the optic nerve, which could prevent arteriolar remodelling [6].

Table 2 Efficacy results at the end of the DAPA-CKD study

	Dapagliflozin		Placebo		HR (CI 95%)	<i>p</i>
	<i>n</i> (%)	Events per 100 patients/year	<i>n</i> (%)	Events per 100 patients/year		
Primary composite variable	197 (9.2)	4.6	312 (14.5)	7.5	0.61 (0.5–0.7)	< 0.001
Decrease in eGFR \geq 50%	112 (5.2)	2.6	201 (9.3)	4.8	0.53 (0.4–0.6)	NA
End-stage renal disease	109 (5.1)	2.5	161 (7.5)	3.8	0.64 (0.5–0.8)	NA
eGFR < 15 ml/min/1.73 m ²	84 (3.9)	1.9	120 (5.6)	2.8	0.67 (0.5–0.8)	NA
Long-term dialysis	68 (3.2)	1.5	99 (4.6)	2.2	0.66 (0.4–0.9)	NA
Kidney transplantation	3 (0.1)	0.1	8 (0.4)	0.2	–	NA
Death due to renal causes	2 (< 0.1)	0.0	6 (0.3)	0.1	–	NA
CV death	65 (3.0)	1.4	80 (3.7)	1.7	0.81 (0.5–1.1)	NA
Composite variable including eGFR decline \geq 50%, end-stage renal disease or death due to renal causes	142 (6.6)	3.3	243 (11.3)	5.8	0.56 (0.4–0.6)	< 0.001
Composite variable including death from CV causes or HF hospitalisation	100 (4.6)	2.2	138 (6.4)	3.0	0.71 (0.5–0.9)	0.009
Death from any cause	101 (4.7)	2.2	146 (6.8)	3.1	0.69 (0.5–0.8)	0.004

CV cardiovascular, HF heart failure, eGFR estimated glomerular filtration rate, NA not applicable (*p*-values for efficacy variables are reported only for outcomes that were included in the hierarchical statistical analysis strategy)

Regarding clinical evidence, a crossover study of 59 people with T2DM looked at changes in retinal capillary flow and arteriolar remodelling after six weeks of treatment with dapagliflozin 10 mg/day or placebo. Dapagliflozin was associated with a reduction in retinal capillary hyperperfusion and a decrease in retinal arteriolar remodelling, factors that contribute to the progression of DR [45]. By using 20-year theoretical models, it has been estimated that the addition of dapagliflozin to

standard therapy would be able to reduce the incidence of DR by approximately 10% over standard therapy [46].

Dapagliflozin Treatment and Non-classical Complications of Diabetes

Macular Oedema

Diabetic macular oedema (DME) is a serious complication, closely related to insulin resistance, capable of seriously threatening visual

acuity in patients with T2DM. It is characterised by a thickening of the macula due to the accumulation of intraretinal or subretinal fluid and exudates [47]. The administration of drugs with diuretic action may be associated with an improvement of DME, which has been used as a theoretical basis for the design of studies evaluating the effect of SGLT2i on DME [7, 47].

In a double-blind trial in 60 patients with clinically significant mild-moderate DME without central involvement, the effect of dapagliflozin vs. placebo on retinal thickness was compared by optical coherence tomography (OCT) [7]. After five months of treatment, there was a significant decrease in retinal thickness in patients with diffuse retinal thickening, but not in patients with other DME [7] patterns. These findings are in line with those reported in small series of patients with DME [47–49]. Thus, in a series of five vitrectomised patients with DME of more than 6 months' duration treated with SGLT2i (four of them with dapagliflozin), improvements were observed at 3, 6 and 12 months of treatment in the median visual acuity index and significant reductions in central retinal thickness [47]. Two other publications, pooling the experience of four patients, also suggest that SGLT2i may improve chronic DME resistant to standard ophthalmic therapy [48, 49].

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) includes a wide range of histological and clinical disorders, ranging from non-alcoholic fatty liver disease to non-alcoholic steatohepatitis (NASH), where inflammation and fibrosis coexist with steatosis and can progress to cirrhosis and hepatocellular carcinoma [8]. Its prevalence is significantly higher in patients with metabolic syndrome or in the presence of some of its components, with an estimated 40–70% of people with T2DM having NAFLD [50]. In recent years, the possible role of SGLT2i as a treatment for NAFLD in patients with diabetes has been evaluated with interest [8].

A meta-analysis of 19 randomised clinical trials analysing more than 15,000 patients with T2DM and NAFLD treated with SGLT2i (six of them with dapagliflozin) found a positive

association between the use of SGLT2i and improvement in biochemical liver function parameters [51]. Similarly, another meta-analysis of 12 clinical trials involving the use of SGLT2i (six of them with dapagliflozin) analysed the effect on liver function and liver fat in 850 patients with obesity and NAFLD (90% with T2DM). After 24 weeks of treatment, there was a significant improvement in both transaminases and liver fat measured by MRI [52]. There is also evidence that the use of dapagliflozin in patients with T2DM and NAFLD with liver fibrosis is able to reduce biomarkers of liver damage, improve hepatic steatosis, and attenuate liver fibrosis, as measured by transient elastography [53, 54].

Several mechanisms have been suggested to explain the beneficial effects of SGLT2i on NAFLD associated with T2DM. Beyond the effect of weight loss and decreased insulin resistance, SGLT2i treatment promotes fatty acid oxidation rather than carbohydrate oxidation, which may contribute to a reduction in fat accumulation and liver inflammation [8].

Cognitive Impairment

Diabetes, cognitive impairment and dementia are prevalent chronic disorders that often coexist in people over 65 years of age [55]. In Alzheimer's disease (AD), alterations in brain glucose metabolism, both in glucose transport and glycolysis (pathophysiological mechanisms common to T2DM and AD [56]), have been observed. A meta-analysis of 28 prospective observational studies showed a 73% increased risk of all types of dementia, a 56% increased risk of Alzheimer's dementia and a 127% increased risk of vascular dementia in patients with T2DM compared to individuals without diabetes [57].

Currently, it is being investigated whether SGLT2i may have a role in the treatment of dementia, especially AD [56]. The strongest theoretical basis supports the neuroprotective effect of SGLT2i through the inhibition of acetylcholinesterase, thus mimicking the mechanism of action of current AD therapies based on inhibitory drugs such as donepezil, rivastigmine or galantamine [9, 55, 56, 58]. Furthermore, SGLT2i could restore the circadian

rhythm of mTOR, a kinase whose chronic activation in T2DM has been associated with the development of lysosomal and mitochondrial dysfunction, preventing the erroneous processing of the amyloid precursor protein and the consequent formation of amyloid plaques in the extraneural space [56]. Finally, the anti-inflammatory properties of SGLT2i could mitigate the oxidative stress-related neuronal loss, while its potential role in angiogenesis and neurogenesis could prevent ischaemia-related brain damage [9].

Although there is currently a clinical trial underway to evaluate the efficacy of dapagliflozin treatment in AD, more clinical evidence on its potential role in the treatment of dementia is needed [59].

Respiratory Disorders During Sleep

The high vascularity of lung parenchyma, together with its richness in collagen and elastin fibres, makes it a potential target for chronic hyperglycaemia [60]. Indeed, there is increasing evidence to suggest that diabetes is associated with decreased lung function and that it exerts a deleterious effect on breathing during sleep [60]. Although evidence is scarce, there are studies suggesting that SGLT2i use may be associated with an improvement in sleep-disordered breathing (SDB), especially obstructive sleep apnoea/hypopnoea syndrome (OSAHS) [10, 61, 62]. In a case-control study of 36 patients with T2DM and OSAHS, the combination of dapagliflozin and metformin was associated with improvements in the apnoea-hypopnoea index, increased minimum oxygen saturation and reduced daytime sleepiness [61]. These changes were not observed in the control group treated with glimepiride and metformin. The authors attribute the improvement in symptoms not only to weight loss but also to changes in body composition and the diuretic effect of dapagliflozin, which may alleviate fluid redistribution from the lower limbs at night [61]. In a series of 30 patients with SDB, treatment with dapagliflozin 5 mg/day was associated with a decrease in the frequency of nocturnal desaturation episodes in those with moderate or severe SDB [10]. Improvement was independent of weight loss

[10]. On the other hand, a meta-analysis including three studies and 65 patients found no difference in the apnoea-hypopnoea index associated with the use of SGLT2i [63]. Although SGLT2i have been proposed as a treatment option for sleep apnoea, more studies are needed to confirm their usefulness [64].

Mismatch Between Evidence and Prescription of SGLT2i

Despite the growing scientific evidence in favour of the use of dapagliflozin and other SGLT2i, there are a large number of patients who still do not benefit from their use [1, 11, 14, 18, 31, 65–68]. In other words, despite the accumulating evidence demonstrating their benefits, their use is not evolving at the same rate. There is no doubt that concerns about the cost of treatment and therapeutic inertia (especially in the field of T2DM, where it takes more than a year to intensify treatment when the patient is out of metabolic control) play a key role in this situation [11, 69, 70] (Table 3).

For instance, in a study conducted between 2013 and 2016 in the US that included more than one million patients with diabetes, it was observed that SGLT2i treatment was started in only 7.2% of patients. Paradoxically, the patients least likely to start SGLT2i were those with previous acute myocardial infarction, heart failure, renal disease, a history of severe hypoglycaemia or those over 75 years of age [71]. Another study, conducted between 2016 and 2019, evaluated hypoglycaemic prescriptions in 382,750 adults with diabetes and established CV disease on metformin [72]. Of these, only 9.3% were receiving any SGLT2i. On this occasion, the factors associated with a greater likelihood of SGLT2i prescription were: age less than or equal to 65 years, being a Caucasian male, having private insurance, and being monitored by an endocrinologist or cardiologist [72]. Similarly, in another cohort study of 21,173 patients with T2DM and CV disease who were analysed between 2013 and 2019, it was observed that only 1.4% received any SGLT2i [73]. Ultimately, these studies show that

Table 3 SGLT2i use in different T2DM patient populations

Study	Country/data source	Period under analysis	Population	n	DDP-4i usage rate (proportion of population)	GLP1 usage rate (proportion of population)	SGLT2i usage rate (proportion of population)
McCoy et al. [71]	United States/ Medicare and insurance company records	2013–2016	Adults with type 1 or 2 DM	1,054,727	9.0%	2.3%	7.2%
Greiver et al. [74]	Australia, Canada, England and Scotland/ primary care records	2012–2017	Adults ≥ 40 years old with T2DM on any hypoglycaemic treatment (excluding insulin alone)	238,619 in 2017	Between 19.1 and 27.6% in 2017	Between 1.9 and 5.6% in 2017	Between 10.1 and 15.3% in 2017
Chahine et al. [72]	United States/electronic medical records	2016–2019	Patients ≥ 18 years old with DM on metformin + CVD (myocardial infarction, coronary heart disease or stroke)	382,750	NR	NR	9.3%
Gunasekaran et al. [75]	United States/ Medicare	September 2016–October 2019	Patients with T2DM + atherosclerotic CVD or heart failure	8448	NR	NR	11%
Hamid et al. [73]	United States/electronic medical records	January 2013–June 2019	Patients ≥ 18 years, old with T2DM and CVD	21,173	6.7%	1.6%	1.4%

T2DM diabetes mellitus type 2, CVD cardiovascular disease, GLP-1 glucagon-like peptide-1 agonist, DDP-4i dipeptidyl peptidase 4 inhibitor, SGLT2i sodium-glucose cotransporter type 2 inhibitor, NR not reported

SGLT2i were initiated more frequently in lower-risk patients who did not have the health conditions that may benefit most from the use of SGLT2i.

Along the same lines, between 2012 and 2017, a cross-sectional, multinational, retrospective observational study conducted on the medical records of 238,619 patients with T2DM observed a decrease in the use of sulphonylureas and an increase in the use of dipeptidyl peptidase 4 (DPP-4) inhibitors (DPP-4i) and SGLT2i, but unevenly. In 2017, between 10.1% and 15.3% of patients were on SGLT2i, while 19.1–27.6% were on DPP-4i [74]. That is, DPP-4i were used more frequently than SGLT2i, despite evidence that SGLT2i are more favourable in preventing adverse cardiovascular outcomes [74].

Ultimately, despite the overwhelming evidence of the benefits of SGLT2i therapy, the prescription rate remains low, especially among the patients most likely to benefit from their cardio-renal protective effects [70]. This evidence–prescription mismatch has contributed to the replacement of linear treatment algorithms based on HbA1c target setting with parallel and independent considerations according to the presence of atherosclerotic CVD or HF [11].

Possible Side Effects Associated with Dapagliflozin

In addition to their demonstrated efficacy, SGLT2i also have a good safety profile [3]. The most common adverse events ($\geq 1/100$ to $< 1/10$) with dapagliflozin include genital and urinary tract infections, rash, polyuria, increased haematocrit, dyslipidaemia and decreased renal creatinine clearance during initial treatment, which is usually reversed. The overall safety profile of dapagliflozin in patients with chronic kidney disease and HF was consistent with the known safety profile of dapagliflozin previously described in studies of the diabetic population.

Other uncommon ($\geq 1/1000$ to $< 1/100$) side effects have been described, including yeast infection, volume depletion, pruritus and thirst, as well as rare ($\geq 1/10,000$ to $< 1/1000$) events

such as diabetic ketoacidosis; in fact, the reported frequency of diabetic ketoacidosis in the DECLARE clinical trial was 0.3% in the dapagliflozin group (vs 0.1% in the placebo group) [15].

The frequency of hypoglycaemia depended on the background treatment used in the clinical study of diabetes mellitus: in the DECLARE, DAPA CKD and DAPA HF studies, no increased risk of severe hypoglycaemia was observed with dapagliflozin therapy compared to placebo (0.7% vs 1.0%; 0.2% vs 0.2%; 0.7% vs 1.3%, respectively) [15, 21, 35]. All cases were reported in patients with T2DM. Taking this into account, safety concerns do not seem to be the reason for the mismatch between evidence and prescription of SGLT2i described here.

DISCUSSION

Dapagliflozin is a SGLT2i that has demonstrated numerous clinical benefits beyond glycaemic control [1]. Although the patients who may benefit the most from treatment with dapagliflozin are those with T2DM and a high CV risk or CV/renal disease, studies and clinical trials on other diabetes-related complications such as DR, macular oedema, NAFLD, sleep apnoea and dementia also suggest a potential benefit of dapagliflozin in these conditions. Although this new evidence has sometimes been obtained from studies with small numbers of participants, it serves to shed light on the wide range of potential beneficial effects that dapagliflozin may exert on patients with T2DM, beyond the classical ones already known. Whether these non-classical benefits are unique to dapagliflozin or should be considered class effects for most SGLT2i remains to be demonstrated.

Despite the evidence presented, the use of SGLT2i in clinical practice is still below 15% in patients with T2DM [11]. Even in patients with a high CV risk, established CV disease, HF or CKD, who could benefit the most from this treatment, the use of dapagliflozin is still really low [72, 73, 75]. This fact is even more striking considering that its use has been approved for any of the above indications when $\text{GFR} \geq 25 \text{ ml/min/1.73 m}^2$, expanding the

proportion of patients who could benefit from dapagliflozin.

CONCLUSIONS

In conclusion, dapagliflozin contributes to the control of CV risk factors and reduces the risk of microvascular complications (nephropathy and retinopathy) and other non-classical complications of T2DM. The underuse of SGLT2i in general and dapagliflozin in particular, even in patients whose profiles suggest that they could greatly benefit from SGLT2i treatment, indicates that greater effort is needed to translate scientific evidence into actual clinical practice to improve patients' quality of life.

ACKNOWLEDGEMENTS

Funding. This study was sponsored by AstraZeneca, including the editorial support and the Rapid Service Fee.

Medical Writing and/or Editorial Assistance. The authors would like to thank Dr. Pablo Rivas and Permanyer Publications Ltd. (Barcelona, Spain) for the editorial support of this study. The authors would also like to thank José Aparicio, member of the medical department of AstraZeneca, for his continuous support during the development of this manuscript.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Author Contributions. The idea for this paper was conceived by Aitziber Izarra and Albert Lecube. The review paper was written by Virginia Bellido, Julia Martínez, Fernando Calvo, Aida Villarroel, Edurne Lecumberri, Juan Moreno, Carlos Morillas, Silvia Rodrigo, Aitziber Izarra and Albert Lecube. The first draft was

compiled and edited by Aitziber Izarra and Albert Lecube. All authors read and approved the final version of this manuscript.

Disclosures. Virginia Bellido, Fernando Calvo, Edurne Lecumberri, Carlos Morillas and Albert Lecube have received fees from AstraZeneca for their participation in expert meetings. Julia Martínez, Aida Villarroel, Silvia Rodrigo, Juan Moreno and Aitziber Izarra are AstraZeneca employees.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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