Diabetes Ther (2022) 13:1281–1298
https://doi.org/10.1007/s13300-022-01280-6

REVIEW

Beyond the Glycaemic Control of Dapagliflozin: Impact on Arterial Stiffness and Macroangiopathy

José M. González-Clemente · María García-Castillo · Juan J. Gorgojo-Martínez · Alberto Jiménez · Ignacio Llorente · Eduardo Matute · Cristina Tejera · Aitziber Izarra · Albert Lecube

Received: March 31, 2022 / Accepted: May 13, 2022 / Published online: June 10, 2022

ABSTRACT

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. In all indications, treatment can be initiated in adults with estimated glomerular filtration rate of at least 25 mL/min/1.73 m^2. As monotherapy or as an additive therapy, dapagliflozin has been shown to promote better glycaemic control, associated with a reduction in body weight and blood pressure in a wide range of patients. In addition, dapagliflozin has a positive impact on

J. M. González-Clemente
Endocrinology and Nutrition Service, Parc Taulí University Hospital, Institute for Research and Innovation Parc Taulí, Universitat Autònoma de Barcelona, Sabadell, Barcelona, Spain

J. M. González-Clemente · A. Lecube
Biomedical Research Networking Center in Diabetes and Associated Metabolic Disorders (CIBERDEM), Carlos III Health Institute, Madrid, Spain

J. M. González-Clemente
e-mail: josmi.gonza@gmail.com

M. García-Castillo · A. Jiménez · E. Matute · A. Izarra
Medical Department, AstraZeneca Spain, Madrid, Spain

M. García-Castillo
e-mail: maria.garciacastillo@astrazeneca.com

A. Jiménez
e-mail: alberto.jimenez@astrazeneca.com

E. Matute
e-mail: Eduardo.matute@astrazeneca.com

A. Izarra
e-mail: Aitziber.izarra@astrazeneca.com

J. J. Gorgojo-Martínez
Endocrinology and Nutrition Unit, Alcorcón Foundation University Hospital, Alcorcón, Madrid, Spain
e-mail: jjgorgojo@fhalcorcon.es

I. Llorente
Endocrinology and Nutrition Service, Nuestra Señora de la Candelaria University Hospital, Canarias, Spain
e-mail: illorentegomez@gmail.com

C. Tejera
Endocrinology and Nutrition Service, Ferrol University Hospital Complex, Ferrol, Spain
e-mail: cristinatejera.mui@gmail.com

A. Lecube (✉)
Endocrinology and Nutrition Service, Arnau de Vilanova University Hospital of Lleida, Avda. Rovira Roure 80, 25198 Lleida, Spain
e-mail: alecube@gmail.com

A. Lecube
Research Group on Obesity, Diabetes and Metabolism (ODIM), Institute of Biomedical Research of Lleida (IRBLleida), University of Lleida, Lleida, Spain

arterial stiffness, helps to control the lipid profile and contributes to a reduced risk of cardiovascular complications. This article reviews the current scientific evidence on the role of dapagliflozin in cardiovascular risk factors including arterial stiffness, cardiovascular disease and heart failure in patients with T2DM, with the aim of helping to translate this evidence into clinical practice. The underuse of SGLT2i in actual clinical practice is also discussed.

Keywords: Dapagliflozin; Sodium–glucose transporter 2 inhibitors; Type 2 diabetes mellitus; Cardiovascular diseases; Heart failure; Therapeutic inertia

Key Summary Points
This article reviews the current scientific evidence on the role of dapagliflozin in cardiovascular risk factors, with the aim of helping to translate this evidence into clinical practice.
Dapagliflozin has been shown to promote better glycaemic control, associated with a reduction in body weight and blood pressure in a wide range of patients.
Dapagliflozin has a positive impact on arterial stiffness, helps to control the lipid profile and contributes to a reduced risk of cardiovascular complications.
In all indications, dapagliflozin treatment can be initiated in adults with estimated glomerular filtration rate of at least 25 mL/min/1.73 m^2.

INTRODUCTION

Dapagliflozin is a reversible and highly selective sodium–glucose cotransporter type 2 inhibitor (SGLT2i) [1, 2]. SGLT2 inhibition by dapagliflozin reduces glucose reabsorption from the glomerular filtrate in the renal proximal tubule with a concomitant reduction in sodium reabsorption, leading to urinary glucose excretion and osmotic diuresis [3, 4]. Dapagliflozin is indicated in adults for the treatment of inadequately controlled type 2 diabetes mellitus (T2DM) in combination with diet and exercise, in monotherapy when metformin is not deemed appropriate, or in addition to other drugs for the treatment of T2DM. Moreover, it is indicated in adults for the treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction (rEF), and for treatment of chronic kidney disease (CKD) with initiation of use in patients with estimated glomerular filtration rate (eGFR) greater than 25 mL/min in all therapeutic indications [3, 4].

In numerous studies, both clinical trials and studies in real clinical practice settings, dapagliflozin has been associated with better glycaemic control, reduced body weight and superior blood pressure (BP) control than its comparators in a wide range of patients [1, 5–8]. Additionally, dapagliflozin has been associated with numerous cardiovascular (CV) and renal benefits and has a robust safety profile [1]. However, despite evidence of its clinical benefit, studies suggest that there are still a large number of patients with T2DM who could benefit from the use of dapagliflozin [9–12].

This article reviews the impact of dapagliflozin on arterial stiffness, cardiovascular risk factors and macroangiopathy in patients with T2DM, with the aim of helping to translate this evidence into clinical practice.

METHODS

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

PubMed was searched for “Dapagliflozin” or “Hypoglycemic Agents” or “Sodium–Glucose Transporter 2 Inhibitors” and “Diabetes Complications” or “Blood Pressure” or “Hypertension” or “Hyperlipidemias” or “Vascular Stiffness” or “Weight Loss” or “Cardiovascular Diseases” or “Acute Coronary Syndrome” or “Peripheral Arterial Disease” or

"Cerebrovascular Disorders" or "Heart Failure". 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. After determining the relevancy of the abstracts, we retrieved and qualitatively assessed complete texts.

Additional references relevant to our review were found by looking through the reference lists of the selected papers.

RESULTS

Cardiovascular Risk Factors

Arterial Stiffness

Adults with T2DM have a two to four times increased risk of developing macrovascular complications compared to adults without diabetes [13]. Hyperglycaemia and insulin resistance are associated with increased arterial stiffness and increased susceptibility of the arterial wall to atherosclerosis. These are independent of age and contribute to the development of CV events in T2DM [13, 14].

Increased arterial stiffness in large elastic arteries such as the aorta results in increased central blood pressure (BP) and blood flow pulsatility. This has deleterious effects on various organs, especially the heart and those highly perfused organs with vascular beds operating at low resistance, such as the brain or kidney [14]. Therefore, arterial stiffness is hypothesised to underlie macro- and microvascular complications of T2DM, constituting a promising therapeutic target in this group of patients [15, 16]. One of the first studies to examine the impact of dapagliflozin on arterial stiffness included 26 patients with T2DM treated for only 2 days. This study demonstrated how acute treatment with dapagliflozin significantly improved systemic endothelial function, arterial stiffness (estimated by calculating the pulse wave velocity between the carotid and femoral arteries) and renal resistance index, independently of BP changes and in the presence of stable natriuresis [17].

In a prospective, observational study involving 32 patients with T2DM treated with dapagliflozin 10 mg/day for 12 months, there was a significant decrease in arterial stiffness independent of changes in blood glucose, uricaemia, BP or weight [18]. Similarly, in another study with 140 patients with T2DM and obesity, 6-month treatment with dapagliflozin produced a statistically significant decrease in aortic arterial stiffness associated with a decrease in body and visceral fat mass, waist/hip ratio and insulin resistance [19]. Finally, in a randomised study of 44 patients with T2DM and 12 weeks of evolution, the effect on arterial stiffness achieved with dapagliflozin 10 mg/day ($n = 24$) and gliclazide 30 mg/day ($n = 20$) was compared. Dapagliflozin was associated with a reduction in vascular stiffness of 11%, accompanied by a decrease in stroke volume of 4%, cardiac output of 5% and mean BP of 5%. The use of gliclazide, on the other hand, did not change any of the aforementioned measurements [5].

Hypertension Control

Hypertension (HT) and T2DM are CV risk factors that act synergistically [20]. There is strong evidence to suggest that dapagliflozin induces a moderate reduction in BP in patients with T2DM, independently of baseline BP, and with a risk of orthostatic reactions similar to placebo [6]. This effect may be explained by the decrease in circulating volume due to its diuretic and natriuretic properties, and is independent of the eGFR [1, 21].

BP lowering associated with dapagliflozin is greater in patients with hypertension than in normotensive subjects [6]. In the aggregate analysis of 13 placebo-controlled clinical trials, BP evolution was assessed in 2360 patients with T2DM treated with dapagliflozin 10 mg/day vs. 2295 patients receiving placebo. In patients with SBP of at least 140 mmHg the mean adjusted decrease in SBP and DBP from baseline to week 24 was − 3.6 mmHg and − 1.2 mmHg in favour of dapagliflozin, respectively [6]. In patients without HT, the decrease in SBP and DBP in favour of dapagliflozin was − 2.6 mmHg and − 1.2 mmHg, respectively. The proportion of patients experiencing orthostatic hypotension was similar between dapagliflozin and

placebo: 6.1% vs. 6.6% in patients with HT and 4.0% vs. 4.2% in patients without hypertension, respectively [6].

BP lowering has also been reported in two large clinical trials with dapagliflozin: DECLARE-TIMI 58 (including patients with CV disease or multiple CV risk factors) [22] and DAPA-HF (in patients with heart failure with reduced ejection fraction, HFrEF) [23, 24] (Tables 1 and 2). In the DECLARE-TIMI 58 study, involving more than 17,000 patients, the mean difference in SBP reduction was 2.7 mmHg [95% confidence interval (95% CI) 2.4–3.0 mmHg], and in DBP 0.7 mmHg (95% CI 0.6–0.9) with dapagliflozin compared to placebo [22]. In the DAPA-HF study, which randomised 4744 patients with symptomatic HF and EF less than 40%, the reduction in SBP with dapagliflozin was -1.92 ± 14.92 mmHg vs. -0.38 ± 15.27 with placebo ($p = 0.002$) [23, 24].

It is worth mentioning that the effects of dapagliflozin on BP are evident as early as the first week after initiation of treatment, and the decrease in SBP is maintained over the long term, at least for 4 years [6, 25]. Similar results with dapagliflozin have also been observed in real-life studies [7, 8].

Dyslipidaemia

The effect of SGLT2i on lipid metabolism has been linked to their ability to regulate key molecules in lipid synthesis, lipid transport and fatty acid oxidation [26]. Most studies show that treatment with dapagliflozin is associated with moderate reductions in triglyceride (TG) levels with elevations in total cholesterol and high-density lipoprotein cholesterol (HDL-C) [27–31]. However, there are also studies, involving a small number of patients, in which these changes have not been seen [32].

Regarding low-density lipoprotein cholesterol (LDL-C), both increases and decreases in its plasma concentration during dapagliflozin treatment have been reported [27, 30, 31]. However, studies that have assessed changes in LDL-C fractions indicate that dapagliflozin treatment is associated with an increase in large, floating LDL particles with lower atherogenic potential, accompanied by a decrease in small, dense LDL particles, which are more associated with CV disease [33]. Recent studies have also described the association between dapagliflozin and a decrease in other markers associated with cardiovascular disease such as the plasma atherogenic index, defined as log(TG/HDL-C), or the triglyceride/glucose (TyG) index [34]. Overall, dapagliflozin would contribute to a less atherogenic lipid profile, by lowering the most atherogenic LDL fractions and increasing HDL-C.

Metabolic Control and Weight Evolution

Several randomised studies have demonstrated the efficacy of dapagliflozin in metabolic control in a broad range of patients with T2DM as well as a good safety profile. Thus, in comparative trials, dapagliflozin showed superiority in HbA1c and weight reduction over glimepiride at 208 weeks, superiority in HbA1c and weight reduction over saxagliptin at 24 weeks, and greater HbA1c and weight reduction compared to placebo in insulin-treated subjects with poor metabolic control. In addition, patients on dapagliflozin had a lower incidence of hypoglycaemia than patients treated with glimepiride and insulin [25, 35]. Similar results have been reported consistently in patients with baseline HbA1c of 9% or above with HT, CV disease, chronic kidney disease and in patients over 65 years of age [1, 36–38].

Regarding monotherapy, in an analysis of six randomised controlled trials involving 2033 patients (with baseline HbA1c between 7.46% and 8.35%), dapagliflozin 10 mg/day for 12–24 weeks was associated with a mean HbA1c reduction of − 0.65% (95% CI − 0.81 to − 0.49) and a weight reduction of − 1.64 kg (95% CI − 1.95 to − 1.33) compared with placebo [39]. Also in poorly controlled patients on metformin monotherapy (mean baseline HbA1c 8.06%), after 102 weeks of follow-up, a − 0.78% reduction in baseline HbA1c was observed with dapagliflozin 10 mg/day, compared to a 0.02% increase with placebo. In combination with other hypoglycaemic agents as additive therapy, dapagliflozin has also been shown to be effective at reducing HbA1c levels [1].

Table 1 Main characteristics of the DECLARE-TIMI 58 study

n	17,160
Intervention	Dapagliflozin 10 mg once a day vs. placebo
Main inclusion criteria	T2D, CVD o risk of suffering from multiple CVRF
HbA1c (%) inclusion criteria	≥ 6.5
Baseline mean HbA1c (%)	8.3
Mean age (years)	64.0
Race (% White)	79.6
Sex (% of men)	62.6
Median duration of T2D (years)	11.0
Median follow-up (years)	4.2
Statins or ezetimibe prescription (%)	75
Metformin prescription (%)	82
Previous CVD/CHF (%)	40/10
Mean HbA1c difference between groups at the end of treatment (%)	− 0.43

DM2 type 2 diabetes mellitus, *CV* cardiovascular, *CVD* established cardiovascular disease, *CVRF* cardiovascular risk factors, *CHF* congestive heart failure

To analyse the dynamics of blood glucose levels throughout the day, a study with 50 patients per arm (with HbA1c between 7.5% and 10.5%) evaluated the effect of dapagliflozin compared to placebo as additive therapy to other hypoglycaemic agents using continuous glucose monitoring. The change in mean 24-h blood glucose was − 18.2 mg/dL with dapagliflozin and + 5.8 mg/dL with placebo. The proportion of time spent in the target glucose range (70–180 mg/dL) was significantly increased with dapagliflozin vs. placebo (69.6% vs. 52.9%; $p < 0.001$) [40].

It is worth noting that approximately two-thirds of the weight loss with dapagliflozin was at the expense of fat mass measured by dual-energy X-ray absorptiometry, while half of the fat lost was visceral fat when measured by MRI [41]. Finally, dapagliflozin has also been associated with significant decreases in uric acid concentrations, an effect that could contribute to the decreased CV risk seen with this drug [42].

Macroangiopathic Complications

Acute Coronary Syndrome

The largest CV safety study of dapagliflozin is DECLARE-TIMI 58 (Table 1) [22]. This study evaluated the effect of dapagliflozin 10 mg/day vs. placebo in 17,160 patients with T2DM and established CV disease (41%) or multiple CV risk factors (59%). After a median follow-up of 4.2 years, dapagliflozin demonstrated non-inferiority to placebo for the composite of cardiovascular death, non-fatal acute myocardial infarction (AMI) and non-fatal stroke (3P-MACE, primary safety endpoint) (Table 3) [22]. In patients with previous AMI ($n = 3584$), dapagliflozin reduced the relative risk of 3P-MACE by 16% and its absolute risk by 2.6% [15.2% vs. 17.8%; hazard ratio (HR) 0.84; 95% CI 0.72–0.99, $p = 0.039$]. This was mainly by decreasing the risk of reinfarction due to type 2 AMI (related to mismatch between myocardial oxygen supply and demand rather than plaque rupture and atherothrombosis), and especially in those patients who started dapagliflozin treatment within 24 months of AMI [43]. However, no benefit was found in patients without previous AMI (7.1% vs. 7.1%; HR 1.00; 95% CI 0.88–1.13; $p = 0.97$) [43].

In terms of real-life studies, the CVD-REAL NORDIC study evaluated 10,227 patients treated with dapagliflozin and 30,681 patients treated with any dipeptidyl peptidase 4 inhibitor (DPP4i) during the period between 2012 and 2015. Dapagliflozin was associated with a lower risk of 3P-MACE (HR 0.79, 95% CI 0.67–0.94), HF (HR 0.62, 95% CI 0.50–0.77) and all-cause mortality (HR 0.59, 95% CI 0.49–0.72) compared with DPP4i. However, the reduction

Table 2 Main characteristics of the DAPA-HF study

n	4744 (1983 with T2D)
Intervention	Dapagliflozin 10 mg once daily vs. placebo
Main inclusion criteria	HF and ejection fraction < 40%. HF functional classification II to IV. With or without T2D
Mean age (years)	66
Race (% White)	70.3
Sex (% of men)	76.6
Median follow-up (years)	1.5
Metformin prescription	51.2% patients with DM2
HF classification (%)	
II	67.5
III	31.5
IV	0.9
Median eGFR (mL/min/1.73 m^2)	66.0 (dapagliflozin)/65.5 (placebo)

CV cardiovascular, *T2D* type 2 diabetes, *ECV* established cardiovascular disease, *CVRF* cardiovascular risk factors, *HF* heart failure, *eGFR* estimated glomerular filtration rate

in AMI was favourable for dapagliflozin but did not reach statistical significance compared with DPP4i (HR 0.91, 95% CI 0.72–1.16) [44]. In another study with 209,867 patients per arm, the use of SGLT2i (30.7% with dapagliflozin) was associated with a lower risk of AMI (5.1% vs. 6.4%; HR 0.82; 95% CI 0.70–0.96) vs. DPP4i, with a similar effect for all SGLT2i [45].

In the CVD-REAL 2 cohort study, with 193,124 patients per arm (60% of those treated with SGLT2i were receiving dapagliflozin), a modest risk reduction against DPP4i was observed for both AMI (HR 0.88, 95% CI 0.80–0.98, $p = 0.020$) and stroke (HR 0.85, 95% CI 0.77–0.93, $p = 0.0004$) [46]. Finally, in another cohort study of more than 200,000 patients (CVD REAL study), the use of SGLT2i (49% of patients on dapagliflozin) was associated with a slightly reduced risk of AMI and stroke compared to other hypoglycaemic agents (insulin, DPP4i, sulfonylureas, glucagon-like peptide 1 agonists or metformin) [47].

These results are in line with a meta-analysis of 14 real-life studies involving more than 3 million patients with T2DM in which the use of SGLT2i is associated with a reduced risk of AMI, stroke, HF, all-cause mortality and CV mortality, but not unstable angina or atrial fibrillation [48].

Peripheral Arterial Disease

A few years ago, concerns were raised about the possible increased risk of lower limb amputations during treatment with SGLT2i [49]. However, a meta-analysis of 27 clinical trials confirmed that dapagliflozin was not associated with an increased risk of peripheral artery disease (PAD) or lower limb amputations [49]. Nor was an increased risk of amputation observed with dapagliflozin in another meta-analysis that included 12 clinical trials and 18 observational studies with SGLT2i [50].

Similarly, the DECLARE-TIMI 58 trial found that people with PAD similarly benefitted from the positive effect of dapagliflozin in terms of reduced CV death, HF hospitalisation and reduced progression of kidney disease, without an increased risk of lower limb events [51].

In real-life studies in a cohort study including 11,431 patients on SGLT2i and 93,972 on DPP4i, the use of SGLT2i was associated with a reduced need for lower limb revascularisation procedures (HR 0.73, 95% CI 0.54–0.98, $p = 0.036$) or amputation (HR 0.43, 95% CI 0.30–0.62, $p < 0.0001$) compared to DPP4i [52]. In conclusion, dapagliflozin is not associated with an increased number of adverse events associated with PAD, either in clinical trials or in real-life studies.

Cerebrovascular Disease

In the DECLARE-TIMI 58 study [22] as well as in a pre-specified meta-analysis of 21 phase 2b/3 clinical trials [53] and the CVD-REAL NORDIC study [44], dapagliflozin showed a neutral effect on stroke risk [22, 53]. However, as in the case of

Table 3 Efficacy results from the DECLARE-TIMI 58 study

	Dapagliflozin (n = 8582)		Placebo (n = 8578)		HR (CI 95%)	p*
	n (%)	Rate per 1000 patients/year	n (%)	Rate per 1000 patients/year		
Primary variables						
Death of CV origin or hospitalisation for HF	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE[a]	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
Secondary variables						
Renal composite variable[b]	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	–
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	–
Other variables analysed						
Hospitalisation for HF	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	–
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	–
Ischaemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	–
Cardiovascular death	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	–
Non-cardiovascular death	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	–
Additional renal composite variable[c]	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	–

CV cardiovascular, *HF* heart failure, *MACE* major adverse cardiac events

*Statistical analysis was developed in a hierarchical manner. So the evaluation of the secondary variables was conditioned to the demonstration of superiority in the two primary co-variables and was only carried out in an exploratory manner

[a]MACE: defined as cardiovascular death, myocardial infarction or ischaemic stroke

[b]Renal composite endpoint defined as at least 40% decrease in eGFR to less than 60 mL/min/1.73 m^2, end-stage kidney disease, or death from renal or cardiovascular causes

[c]Additional renal composite endpoint defined as at least 40% decrease in eGFR to less than 60 mL/min/1.73 m^2, end-stage kidney disease, or renal death

AMI, in other large real-life cohort studies, dapagliflozin was associated with a reduced risk of stroke compared with DPP4i (CVD-REAL 2: HR 0.85; 95% CI 0.77–0.93, $p = 0.0004$) or overall with other hypoglycaemic agents (CVD-REAL: HR 0.83; 95% CI 0.71–0.97, $p = 0.02$) [46, 47]. Similarly, in a meta-analysis of 14 real-life studies involving more than 3 million patients, the use of SGLT2i was associated with a significant reduction in the risk of stroke [48].

Experimental studies have suggested that this protective effect of SGLT2i against stroke is mediated by its antioxidant and anti-inflammatory effects, by anti-apoptotic mechanisms and the production of ultrastructural enhancements in neurons and at the blood–brain barrier [54].

Heart Failure

Up to 50% of people with T2DM may develop HF [55]. The major advance in recent years related to dapagliflozin is the demonstration of its clinical benefits for the treatment of HFrEF, both in people with and without T2DM [22, 24]. In the DECLARE-TIMI 58 study, dapagliflozin 10 mg/day showed superiority over placebo in preventing the composite endpoint of HF hospitalisation or CV death (4.9% vs. 5.8%; HR

0.83, 95% CI 0.73–0.95, $p = 0.005$) (Table 3). Exploratory analysis of the components of the composite variable revealed that the difference in treatment effect was mainly due to HF hospitalisation (HR 0.73, 95% CI 0.61–0.88). The benefit was observed in patients with and without established CV disease, with or without baseline HF and in those with HF with reduced or preserved EF, and was consistent across subgroups including age, sex, renal function and region [22, 56].

The benefit of dapagliflozin in the treatment of HFrEF was confirmed in the DAPA-HF study, a phase 3 trial in which 4744 patients (42% with T2DM) with symptomatic HF and EF less than 40% (functional class II to IV) were randomised to receive dapagliflozin 10 mg/day or placebo, added to standard HF therapy (Tables 2 and 4) [23, 57–59]. After a median follow-up of 18.2 months, the primary composite endpoint, which included HF worsening (hospitalisation or urgent visit leading to intravenous therapy for HF) or CV death, occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and 502 of 2371 patients (21.2%) in the placebo group (HR 0.74; 95% CI 0.65–0.85, $p < 0.001$), resulting in a relative risk reduction with dapagliflozin of 26%. In this case, both worsening HF (10.0% vs. 13.7%; HR 0.70, 95% CI 0.59–0.83) and CV death (9.6% vs. 11.5%; HR 0.82, 95% CI 0.69–0.98) were significantly lower in the dapagliflozin-treated group [23]. The benefit was observed in both people with and without T2DM, and it is worth highlighting that the benefit with dapagliflozin on the primary endpoint reached statistical significance as early as 28 days after the start of treatment [58, 59]. Furthermore, the greatest benefits occurred in patients with a history of HF hospitalisation in the 12 months prior to baseline. Dapagliflozin was also associated with improved symptoms, function, quality of life and overall health status in people with HF and reduced EF [58].

A meta-analysis, including nine randomised clinical trials with dapagliflozin in patients with structural heart disease and HF (EF less than or equal to 50%, NYHA classification I or higher, or NT-proBNP 600 pg/mL or higher), confirmed the beneficial effect in terms of decreased risk of HF hospitalisation [relative risk (RR) 0.72; 95% CI 0.63–0.83], CV death (RR 0.80; 95% CI 0.68–0.93), and all-cause mortality (HR 0.83; 95% CI 0.71–0.71) [60]. Similar results are observed in patients with chronic kidney disease as demonstrated by the DAPA-CKD trial, which included 68% of patients with T2DM. In this study, dapagliflozin was associated with a 29% reduction in the risk of hospitalisation for HF or CV death, mainly due to a decrease in HF hospitalisations (Tables 5 and 6) [61].

The beneficial effects of dapagliflozin and other SGLT2i on the risk of HF hospitalisation in patients with T2DM and their superiority to other hypoglycaemic agents have also been confirmed in real life, even including patients with no previous diagnosis of HF [45, 46, 48, 62, 63]. The use of dapagliflozin in patients with preserved EF or acute HF is being evaluated in the DELIVER and DICTATE AHF studies, respectively [64, 65]. Meanwhile, international societies such as the American Diabetes Association (ADA) [55], the American College of Cardiology (ACC) [66] or the European Society of Cardiology (ECS) [67] advise the preferential use of SGLT2i in people with T2DM and HF with reduced EF. Among the aetiopathogenic mechanisms that would help explain the beneficial effect of dapagliflozin on heart failure, the following should be highlighted: (i) metabolic effects, including reduction of glucotoxicity, visceral fat or uric acid, as well as an increase in haematocrit; (ii) haemodynamic effects, especially osmotic diuresis and natriuresis reducing preload (volaemia) and afterload (blood pressure) while improving glomerulotubular balance; and (iii) direct effects on the myocardium, encompassing the increase of beta-hydroxybutyrate (more efficient for myocardial disease as an energy source than glucose or fatty acids), the direct inhibitory effect on myocardial sodium–hydrogen exchanger type 1 (NHE-1) favouring calcium entry into the mitochondria, or the reduction of pro-inflammatory adipokines derived from epicardial and perivascular fat [68].

Table 4 Efficacy outcomes of the DAPA-HF study

	Dapagliflozin (n = 2373)		Placebo (n = 2371)		HR (CI 95%)	p
	n (%)	Rate per 1000 patients/ year	n (%)	Rate per 1000 patients/ year		
Primary variable						
Composite variable[a]	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65–0.85)	< 0.001
Hospitalisation or urgent visit due to HF	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59–0.83)	NA
HF hospitalisation	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59–0.83)	NA
Urgent visit due to HF	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20–0.90)	NA
CV-related death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69–0.98)	NA
Secondary variables; n (%)						
CV death or HF hospitalisation	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65–0.85)	< 0.001
Total number of HF hospitalisations and CV deaths	567	–	742	–	–	< 0.001
Change in KCCQ symptom index total score at 8 months	6.1 ± 18.6	–	3.3 ± 19.2	–	1.18 (1.11–1.26)	< 0.001
Worsening kidney function[b]	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44–1.16)	NA
Death from any cause	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71–0.97)	NA

CV cardiovascular, *HF* heart failure, *KCCQ* Kansas City Cardiomyopathy Questionnaire (a higher score indicates fewer symptoms), *NA* not applicable because p values for effectiveness outcomes are reported only for outcomes that were included in the hierarchical evaluation strategy

[a]Primary composite variable defined as worsening HF (hospitalisation or an urgent visit resulting in IV therapy) or death from cardiovascular causes

[b]Worsening kidney function is a composite variable that includes a 50% or greater reduction in eGFR sustained for at least 28 days, end-stage renal disease, or death from renal causes

DISCUSSION

In this review we show evidence of the clinical benefit of dapagliflozin beyond glycaemic control in clinical trials and in real practice studies (Table 7). However, in daily practice, we may not be doing it right.

Therapeutic inertia is common in the field of T2DM [69]. The evidence shown in this review suggests that the use of dapagliflozin is associated with numerous clinical benefits beyond glycaemic control, facilitating the control of CV risk factors and decreasing the incidence of CV events. However, SGLT2i are a family of drugs that are underutilised in actual clinical practice in patients with T2DM [9–12, 70]. In the context of cardiology, there is also a risk of underuse of dapagliflozin for the treatment of HFrEF [71].

An analysis of 1,054,727 patients with T2DM in the USA, conducted between 2013 and 2016, showed that only 7.2% initiated new treatment with any SGLT2i [11]. Patients less likely to initiate this therapy were those with previous

Table 5 Main baseline characteristics of participants in the DAPA-CKD study

n	4304
Intervention	Dapagliflozin 10 mg/day vs. placebo
Main inclusion criteria	Adults with or without DM2; eGFR 25–75 mL/min/1.73 m^2; CAC 200–5000 mg/g
Median follow-up (years)	2.4
Participants with DM2	2906 (67.5)
Age (years)	61.8 ± 12.1
Males	2852 (66.3)
Caucasian	2290 (53.2)
Cardiovascular disease	1610 (37.4)
eGFR (mL/min/1.72 m^2)	43.1 ± 12.4
CAC median (mg/g)	949
Previous medication	
ACE inhibitors	1354 (31)
ARA2	2870 (66)
Diuretics	1882 (43)
Statin	2758 (64)

Data expressed as median, mean ± standard deviation or total number (percentage)

eGFR estimated glomerular filtration rate, *ARA2* angiotensin receptor antagonist type 2, *DM2* diabetes mellitus type 2, *ACE* angiotensin-converting enzyme, *ARA* aldosterone receptor antagonists, *CAC* urine albumin/creatinine ratio

AMI, HF, renal disease, severe hypoglycaemia, and those over the age of 75 or black [11].

Along the same lines, in a multinational cohort study of over 238,619 patients with T2DM, a decrease in the use of sulfonylureas and an increase in DPP4i and SGLT2i was observed between 2012 and 2017. However, in 2017 only 10.1–15.3% of patients were on SGLT2i while 19.1–27.6% were on some DPP4i [72]. A more recent study conducted between 2016 and 2019 evaluated hypoglycaemic prescriptions in adults with T2DM who were receiving metformin and had established CV disease (ischaemic heart disease or stroke, excluding patients with stage 4 and 5 chronic kidney disease). Regarding the 383,750 patients identified, only 9.5% were receiving SGLT2i. Factors associated with a higher likelihood of SGLT2i prescription were age less than or equal to 65 years, being male and Caucasian, having private insurance, or consulting with an endocrinologist or cardiologist [73]. Similarly, in another cohort study of more than 20,000 patients with T2DM and established CV disease, analysed between 2013 and 2019, only 1.4% were found to receive SGLT2i [9].

Several factors could be contributing to the low rate of SGLT2i prescription, including therapeutic inertia or concerns about treatment cost [74]. Although in the case of HF, evidence suggests that dapagliflozin is likely to be a cost-effective therapy for the treatment of HF with reduced EF in the UK, German and Spanish healthcare systems [59].

CONCLUSIONS

In short, dapagliflozin is a treatment that has shown long-term efficacy and safety as an oral antidiabetic, but also has numerous clinical benefits beyond glycaemic control [1]. Dapagliflozin can reduce arterial stiffness in people with T2DM, which is associated with an increased susceptibility to atherosclerosis regardless of age [18]. Dapagliflozin is also associated with a significant decrease in BP [6] and a favourable lipid profile, producing a decrease in the most atherogenic LDL fractions and an increase in HDL-C [6, 33].

As for macroangiopathy, the strongest findings suggest that dapagliflozin significantly reduces the risk of 3P-MACE, mainly mediated by a decreased risk of reinfarction in patients with a previous infarction [43]. In reducing the risk of AMI or stroke, dapagliflozin may have a

Table 6 Efficacy results at the end of the DAPA-CKD study

	Dapagliflozin (n = 2152)		Placebo (n = 2152)		HR (CI 95%)	p^*
	n (%)	Events per 100 patients/year	n (%)	Events per 100 patients/year		
Primary variables						
Composite primary variable	197 (9.2)	4.6	312 (14.5)	7.5	0.61 (0.51–0.72)	< 0.001
Decreased eGFR ≥ 50%	112 (5.2)	2.6	201 (9.3)	4.8	0.53 (0.42–0.67)	NA
Terminal kidney disease	109 (5.1)	2.5	161 (7.5)	3.8	0.64 (0.50–0.82)	NA
eGFR < 15 mL/min/1.73 m^2	84 (3.9)	1.9	120 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis	68 (3.2)	1.5	99 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation	3 (0.1)	0.1	8 (0.4)	0.2	–	NA
Kidney-related death	2 (< 0.1)	0.0	6 (0.3)	0.1	–	NA
Cardiovascular-related death	65 (3.0)	1.4	80 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary variables						
Composite variable that includes reduced eGFR ≥ 50%, terminal kidney disease or kidney-related death	142 (6.6)	3.3	243 (11.3)	5.8	0.56 (0.45–0.68)	< 0.001
Composite variable that includes cardiovascular-related death or HF hospitalisation	100 (4.6)	2.2	138 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any causes	101 (4.7)	2.2	146 (6.8)	3.1	0.69 (0.53–0.88)	0.004

CV cardiovascular, *HF* heart failure, *eGFR* estimated glomerular filtration rate

*NA: not applicable because p values for efficacy variables are informed only for results that were included in the hierarchical statistical analysis strategy

neutral or slightly protective effect relative to other hypoglycaemic agents as indicated by real-life studies. Furthermore, there is no evidence that dapagliflozin worsens the progression of PAD or the risk of amputation [50].

Furthermore, dapagliflozin is associated with an improvement in symptoms, quality of life and a reduction in the risk of hospital admission in people with HF and reduced EF, regardless of the presence of T2DM and from an eGFR of at

Table 7 Summary of the main benefits of dapagliflozin on arterial stiffness, cardiovascular risk factors and macroangiopathy in patients with T2DM

Benefits beyond glycaemic control	Main evidence
Reduction in arterial stiffness in patients with T2DM	Hidalgo Santiago et al. [18], Hong [19], van Bommel [5]
CV risk factor control	
Blood pressure lowering greater in patients with T2D and hypertension than in normotensive subjects	Sjöström et al. [6]
Blood pressure lowering in patients with T2MD and CV disease or multiple CV risk factors	DECLARE-TIMI 58 trial [22]
Blood pressure lowering in patients with T2MD and HFrEF	DAPA-HF trial [23, 24]
Blood pressure lowering in patients with T2MD in real-life studies	McGurnaghan et al. [7], Morieri et al. [8]
Improvement in lipid profile by lowering the most atherogenic LDL fractions and increasing HDL-C in patients with T2DM	Hayashi et al. [33], Imre [34]
Weight loss mainly at the expense of fat mass	Bolinder et al. [41]
Lowering of uric acid concentrations	Bailey [42]
Reduction of macroangiopathic complications	
Reduction in the risk of 3P-MACE (mainly by decreasing the risk of reinfarction) in patients with T2DM and previous AMI	DECLARE-TIMI 58 trial [22, 43]
Lower risk of 3P-MACE, hospitalisation for heart failure and all-cause mortality compared with DPP4i in real-life studies	CVD-REAL NORDIC study [44]
Lower risk of AMI compared with DPP4i in real-life studies	Canadian Network for Observational Drug Effect Studies (CNODES) [45]
Lower risk of AMI and stroke compared with DPP4i in real-life studies	CVD-REAL 2 study [46]
Lower risk of AMI and stroke compared with other hypoglycaemic agents (insulin, DPP4i, sulfonylureas, glucagon-like peptide 1 agonists or metformin) in real-life studies	CVD-REAL study [47]
Reduction in the risk of AMI, stroke, HF, all-cause mortality and CV mortality in meta-analysis of real-life studies with SGLT2i	Li et al. [48]
Lower risk of lower limb revascularisation or amputation compared with DPP4i in real-life studies	Lee et al. [52]

Table 7 continued

Benefits beyond glycaemic control	Main evidence
Prevention of HF hospitalisation/CV death in patients with and without established CV disease, with or without baseline HF and in those with HF with reduced or preserved EF	DECLARE-TIMI 58 trial [22, 56]
Prevention of HF hospitalisation/CV death in people with and without T2DM	DAPA-HF trial [23, 57–59]
Reduction in the risk of hospitalisation for HF/CV death in patients with chronic kidney disease with or without T2DM	DAPA-CKD trial [61]
Decreased risk of HF hospitalisation, CV death and all-cause mortality in patients with structural heart disease and HF in meta-analysis of randomised clinical trials (patients with or without T2DM)	Cai et al. [60]

3P-MACE composite outcome defined as the first occurrence of cardiovascular death, non-fatal acute myocardial infarction or non-fatal stroke, *AMI* non-fatal acute myocardial infarction, *CV* cardiovascular, *HDL-C* high-density lipoprotein cholesterol, *HFrEF* heart failure with reduced ejection fraction, *SGLT2i* sodium glucose cotransporter type 2 inhibitor, *T2DM* type 2 diabetes mellitus

least 25 mL/min/1.73 m^2, and has also been incorporated into the therapeutic arsenal for HFrEF [55, 66, 67]. Although the use of SGLT2i in clinical practice is below 10% in patients with T2DM, an increase in its prescription is expected in the coming years. Given the large and compelling evidence of the clinical benefit of dapagliflozin, we recommend the generalization of its use to all patients with T2DM who meet the indications.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Pablo Rivas and Permanyer for the editorial support of this study as well as José Aparicio, member of AstraZeneca's medical department for his continuous support during the development of this manuscript.

Funding. This study and the journal's Rapid Service Fee was sponsored by AstraZeneca.

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 as a whole, and have given their approval for this version to be published.

Author Contributions. José M. González-Clemente/María García-Castillo: Review of the literature, drafting of the sections: Arterial stiffness and Acute Coronary Syndrome. Ignacio Llorente Gómez-Segura/Eduardo Matute-Troncoso: Review of the literature, drafting of the sections: Cerebrovascular disease and therapeutic inertia. Juan J. Gorgojo-Martínez/Alberto Jiménez-Buiza: Review of the literature, drafting of the sections: Heart Failure and metabolic control. Cristina Tejera-Pérez/Alberto Jiménez-Buiza: Review of the literature, drafting of the sections: Peripheral Arterial Disease and BP control. Albert Lecube-Torelló/Aitziber Izarra-Navarro: Review of the literature, drafting of the Dyslipidaemia section, as well as revision of the manuscript.

Disclosures. José M. González-Clemente, Juan J. Gorgojo-Martínez, Ignacio Llorente Gómez-Segura, Cristina Tejera-Pérez, and Albert Lecube-Torelló have received fees from AstraZeneca for their participation in expert meetings. María García-Castillo, Alberto Jiménez-Buiza, Eduardo Matute-Troncoso and Aitziber Izarra-Navarro are AstraZeneca employees.

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

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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