

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

José Miguel González-Clemente<sup>1,2</sup>, María García<sup>3</sup>, Juan José Gorgojo<sup>4</sup>, Alberto Jiménez<sup>3</sup>, Ignacio Llorente<sup>5</sup>, Eduardo Matute<sup>3</sup>, Cristina Tejera<sup>6</sup>, Aitziber Izarra<sup>3</sup> and Albert Lecube<sup>2,7\*</sup>

<sup>1</sup>Endocrinology and Nutrition Department, Parc Taulí University Hospital, Institute for Research and Innovation Parc Taulí, Universitat Autònoma de Barcelona, Sabadell, Barcelona, Spain.

<sup>2</sup>Biomedical Research Networking Center in Diabetes and Associated Metabolic Disorders (CIBERDEM), Carlos III Health Institute, Madrid, Spain.

<sup>3</sup>AstraZeneca Spain, Medical Department, Madrid, Spain.

<sup>4</sup>Endocrinology and Nutrition Unit, Alcorcón Foundation University Hospital, Alcorcón, Madrid, Spain.

<sup>5</sup>Endocrinology and Nutrition Department, Nuestra Señora de la Candelaria University Hospital, Canarias, Spain.

<sup>6</sup>Endocrinology and Nutrition Department, Ferrol University Hospital Complex, Ferrol, Spain.

<sup>7</sup>Endocrinology and Nutrition Department, Arnau de Vilanova University Hospital, Lleida, Research Group on Obesity, Diabetes and Metabolism (ODIM), Institute of Biomedical Research of Lleida (IRBLleida), University of Lleida, Spain.

Received: December 10, 2021; Accepted: February 05, 2022; Published: February 25, 2022

\*Corresponding author: Albert Lecube, Ph.D., M.D, Endocrinology and Nutrition Service, Arnau de Vilanova University Hospital of Lleida, Avda. Rovira Roure 80, 25198 Lleida. Phone: +34 973 705 183; E-mail: alecube@gmail.com

## 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  $\geq 25$  ml/min/1.73 m<sup>2</sup>. 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 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 to help translating this evidence into clinical practice. The underuse of SGLT2i in actual clinical practice is also discussed.

**Key words:** Dapagliflozin; Sodium-Glucose Transporter 2 Inhibitors; Type 2 Diabetes Mellitus; Cardiovascular Diseases; Heart Failure; Therapeutic Inertia.

## 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]. 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 GFR greater than 25 ml/min in all therapeutic indications [3].

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 [1,4–7]. 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 [8–11].

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.

## Cardiovascular risk factor

### Arterial stiffness

Adults with T2DM have a two to four times increased risk of developing macrovascular complications compared to adults without diabetes[12]. 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[12,13].

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[13]. Therefore, arterial stiffness is hypothesized to underlie macro and microvascular complications of T2DM, constituting a promising therapeutic target in this group of patients[14,15]. One of the first studies to examine the impact of dapagliflozin on arterial stiffness included 26 patients with T2DM treated for only two 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[16].

In a prospective, observational study involving 32 patients with T2DM treated with dapagliflozin 10mg/day for 12 months, there was a significant decrease in arterial stiffness independent of changes in blood glucose, uricaemia, BP or weight[17]. Similarly, 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[18]. 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 above measurements[4].

### Hypertension control

Hypertension (HT) and T2DM are CV risk factors that act synergistically[19]. So far 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[5]. This effect may be explained by the decrease in circulating volume due to its diuretic and natriuretic properties, and is independent of the estimated glomerular filtration rate[1,20].

BP lowering associated with dapagliflozin is greater in patients

with hypertension than in normotensive subjects[5]. In the aggregate analysis of 13 placebo-controlled clinical trials, BP evolution was assessed in 2,360 patients with T2DM treated with dapagliflozin 10 mg/day vs. 2,295 patients receiving placebo. In patients with SBP  $\geq$  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[5]. 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 non-hypertensive patients, respectively[5].

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)[21] and DAPA-HF (in patients with HFrEF)[22,23] (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[21]. In the DAPA-HF study, which randomised 4,744 patients with symptomatic HF and EF less than 40%, the reduction in SBP with dapagliflozin was  $-1.92 \pm 14.92$  mmHg vs.  $-0.38 \pm 15.27$  with placebo (p=0.002)[22,23].

n	17,160
Intervention	Dapagliflozin 10 mg once a day vs. placebo
Main inclusion criteria	T2D, CVD or risk of suffering from multiple CVRF
HbA1c (%) inclusion criteria	$\geq$ 6,5
Baseline mean HbA1c (%)	8,3
Mean age (years)	64
Race (% White)	79.6
Sex (% of men)	62.6
Median duration of T2D (years)	11
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
T2DM: type 2 diabetes; CV: cardiovascular; ECV: established Cardiovascular Disease; CVRF: cardiovascular Risk Factors; CHF: congestive Heart Failure.	

**Table 2: Main characteristics of the DAPA-HF study.**

n	4.744 (1.983 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 <sup>2</sup> )	66.0 (dapagliflozin) / 65.5 (placebo)
CV: cardiovascular; T2DM: type 2 diabetes; ECV: established Cardiovascular Disease; CVRF: cardiovascular Risk Factors; HF: heart Failure; eGFR: estimated Glomerular Filtration Rate.	

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[5,24]. Similar results with dapagliflozin have also been observed in real-life studies[6,7].

**Dyslipidemia**

The effect of SGLT2i on lipid metabolism have been linked to their ability to regulate key molecules in lipid synthesis, lipid transport and fatty acid oxidation[25]. 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) [26–30]. However, there are also studies, involving a small number of patients, in which these changes have not been seen[31].

Regarding low-density lipoprotein cholesterol (LDL-C), both increases and decreases in its plasma concentration during dapagliflozin treatment have been reported[26,29,30]. 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[32]. 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[33]. 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[24,34]. Similar results have been reported consistently in patients with baseline HbA1c ≥ 9% with HT, CV disease, chronic kidney disease and in patients over 65 years of age[1,35–37].

Regarding monotherapy, in an analysis of six randomised controlled trials involving 2,033 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[38]. 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].

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-hour 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)[39].

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[40]. 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[41].

## Macroangiopathic complications

### Acute coronary syndrome

The largest CV safety study of dapagliflozin is DECLARE-TIMI 58 (Table 1)[21]. 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)[21]. In patients with previous AMI (n=3,584), 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[42]. 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)[42].

**Table 3: Efficacy results from the DECLARE-TIMI 58 study.**

	Dapagliflozin (n=8,582)		Placebo (n=8,578)		HR (IC95%)	p*
	n (%)	Rate per 1,000 patients/year	n (%)	Rate per 1,000 patients/year		
<b>Primary variables</b>						
Death of CV origin or hospitalization 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
<b>Secondary variables</b>						
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)	-
<b>Other variables analyzed</b>						
Hospitalization 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)	-
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	-
Cardiovascular death	245 (2.9)	7	249 (2.9)	7.1	0.98 (0.82–1.17)	-
Non-cardiovascular death	211 (2.5)	6	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	0.53 (0.43–0.66)	-

CV: cardiovascular; HF: heart Failure; MACE: major adverse cardiac events.

<sup>a</sup>MACE: defined as cardiovascular death, myocardial infarction or ischemic stroke.

<sup>b</sup>Renal composite endpoint defined as  $\geq 40\%$  decrease in eGFR to  $< 60$  mL/min/1.73 m<sup>2</sup>, end-stage kidney disease, or death from renal or cardiovascular causes.

<sup>c</sup>Additional renal composite endpoint defined as  $\geq 40\%$  decrease in eGFR to  $< 60$  mL/min/1.73 m<sup>2</sup>, end-stage kidney disease, or renal death.

\* 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.

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 (DPP-4) inhibitor 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 (41). However, the reduction in AMI was favourable for dapagliflozin but did not reach statistical significance compared with DPP4i (HR 0.91, 95% CI 0.72-1.16)[43]. 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% v 6.4%; HR 0.82; 95% CI 0.70-0.96) vs. DPP4i, with a similar effect for all SGLT2i[44].

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,  $p=0.0004$ )[45]. 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, sulphonylureas, glucagon-like peptide 1 agonists or metformin)[46].

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[47].

### Peripheral arterial disease

A few years ago, concerns were raised about the possible increased risk of lower limb amputations during treatment with SGLT2i[48]. 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[48]. 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[49].

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 hospitalization and reduced progression of kidney disease, without an increased risk of lower limb events[50].

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[51]. In conclusion, dapagliflozin is not associated with an increased number of adverse events associated with peripheral arterial disease, neither in clinical trials nor in real-life studies.

### Cerebrovascular disease

In the DECLARE-TIMI 58 study[21] as well as in a pre-specified meta-analysis of 21 phase 2b/3 clinical trials[52] and the CVD-REAL NORDIC study[43], dapagliflozin showed a neutral effect on stroke risk[21,52]. However, as in the case of 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,  $p=0.02$ )[45,46]. 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[47].

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[53].

### Heart failure

Up to 50% of people with T2DM may develop HF[54]. 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[21,23]. In the DECLARE-TIMI 58 study, dapagliflozin 10 mg/day showed superiority over placebo in preventing the composite endpoint of HF hospitalization or CV death (4.9% vs. 5.8%; HR 0.83, 95% CI 0.73 to 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 hospitalization (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[21,55].

The benefit of dapagliflozin in the treatment of HFrEF was confirmed in the DAPA-HF study, a phase 3 trial in which 4,744 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)[22,56–58]. After a median follow-up of 18.2 months, the primary composite endpoint, which included HF worsening (hospitalization or urgent visit leading to intravenous therapy for HF) or CV death, occurred in 386 of 2,373 patients (16.3%) in the dapagliflozin group and 502 of 2,371 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[22]. 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[57,58].

**Tabla 4. Resultados de eficacia del estudio DAPA-HF.**

	Dapagliflozin (n=8,582)		Placebo (n=8,578)		HR (IC95%)	p
		Rate per 1000 patients/year		Rate per 1000 patients/year		
<b>Primary variable (n [%])</b>						
Composite variable	386 (16.3)	11.6	502 (21.2)	15.6	0.74(0.65 a 0.85)	<0.001
Hospitalisation or urgent visit due to HF	237 (10.0)	7.1	326 (13.7)	10.1	0.7(0.59 a 0.83)	NA
HF hospitalisation	231 (9.7)	6.9	318 (13.4)	9.8	0.7(0,59 a 0,83)	NA
Urgent visit due to HF	10 (0.4)	0.3	23 (1.0)	0.7	0.43(0.20 a 0.90)	NA
CV-related death	227 (9.6)	6.5	273 (11.5)	7.9	0.82(0.69 a 0.98)	NA
<b>Secondary variables (n [%])</b>						
CV death or HF hospitalisation	382 (16.1)	11.4	495 (20.9)	15.3	0.75(0.65 a 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 ±1 8.6	-	3.3 ± 19.2	-	1.18(1.11 a 1.26)	<0.001
Worsening kidney function <sup>b</sup>	28 (1.2)	0.8	39 (1.6)	1.2	0.71(0.44 a 1.16)	NA
Death from any cause	276 (11.6)	7.9	329 (13.9)	9.5	0.83(0.71 a 0.97)	NA

CV: cardiovascular; IC: insuficiencia cardiaca; KCCQ: *kansas City Cardiomyopathy Questionnaire* (una puntuación más alta indica menos síntomas); NA: No aplicable porque los valores de p para los resultados de eficacia se informan solo para los resultados que se incluyeron en la estrategia de evaluación jerarquizada.

<sup>a</sup>Variable primaria compuesta definida como empeoramiento de la IC (hospitalización o una visita urgente que resulta en terapia intravenosa para la IV) o muerte por causas cardiovasculares.

<sup>b</sup>El empeoramiento de la función renal es una variable compuesta que incluye una reducción del 50% o más en la TFGe sostenida durante al menos 28 días, enfermedad renal terminal o muerte por causas renales.

Furthermore, the greatest benefits occurred in patients with a history of HF hospitalization 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[57].

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 NT-proBNP ≥ 600 pg/mL), confirmed the beneficial effect in terms of decreased risk of HF hospitalization [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 [hazard ratio 0.83; 95% CI 0.71-0.71]. 83; 95% CI 0.71-0.97[59]. 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 hospitalization for HF or CV death, mainly due to a decrease in HF hospitalizations[60].

The beneficial effects of dapagliflozin and other SGLT2i on the risk of HF hospitalization 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[44,45,47,61,62]. The use of dapagliflozin in patients with preserved EF or acute HF is being evaluated in the DELIVER and DICTATE AHF studies, respectively[63,64]. Meanwhile, international societies such as the American Diabetes Association (ADA)[54], the American College of Cardiology (ACC)[65] or the European Society of Cardiology (ECS)[66] 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 (volemia) 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[73].

**“We are not doing it right”**

Therapeutic inertia is common in the field of T2DM[67]. 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[8–11,68]. In the context of cardiology, there is also a risk of underuse of dapagliflozin for the treatment of HFrEF[69].

An analysis of 1,054,727 patients with T2DM in the United States, conducted between 2013 and 2016, showed that only 7.2% initiated new treatment with any SGLT2i[10]. Patients less likely to initiate this therapy were those with previous AMI, HF, renal disease, severe hypoglycaemia, and those over the age of 75 or black[10].

Along the same lines, in a multinational cohort study of over 238,619 patients with T2DM, a decrease in the use of sulphonylureas and an increase in DPP4i and SGLT2i was observed between 2012 and 2017. However, in 2017 only 10.1% to 15.3% of patients were on SGLT2i while 19.1% to 27.6% were on some DPP4i[70]. 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[71]. 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[8].

Several factors could be contributing to the low rate of SGLT2i prescription, including therapeutic inertia or concerns about treatment cost[72]. 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[58].

## Conclusion

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 [17]. Dapagliflozin is also associated with a significant decrease in BP5 and a favourable lipid profile, producing a decrease in the most atherogenic LDL fractions and an increase in HDL-C [5,32].

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 [42]. In reducing the risk of AMI or stroke, dapagliflozin may have a 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 [49].

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 estimated glomerular filtration rate  $\geq 25$  ml/min/1.73m<sup>2</sup>, and has also been incorporated into the therapeutic arsenal for HFrEF[57,65,66]. Albeit 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.

## 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.

## Conflict of interests

José Miguel González-Clemente, Juan José Gorgojo, Ignacio Llorente, Cristina Tejera and Albert Lecube have received fees from AstraZeneca for their participation in expert meetings.

María García, Alberto Jiménez, Eduardo Matute and Aitziber Izarra are AstraZeneca employees.

## Funding Source

This study was sponsored by AstraZeneca.

## References

1. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. *Drugs*. 2019;79(10):1135-1146. doi: 10.1007/s40265-019-01148-3.
2. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab*. 2012;14(1):83-90. doi: 10.1111/j.1463-1326.2011.01517.x.
3. Ficha técnica Forxiga.
4. van Bommel EJM, Smits MM, Ruiter D, Muskiet MHA, Kramer MHH, Nieuwdorp M, et al. Effects of dapagliflozin and gliclazide on the cardiorenal axis in people with type 2 diabetes *J Hypertens*. 2020 ;38(9):1811-1819. doi: 10.1097/HJH.0000000000002480.
5. Sjöström CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. *Diab Vasc Dis Res*. 2015;12(5):352-358. doi: 10.1177/1479164115585298.

6. McGurnaghan SJ, Brierley L, Caparrotta TM, McKeigue PM, Blackburn LAK, Wild SH, et al. The effect of dapagliflozin on glycaemic control and other cardiovascular disease risk factors in type 2 diabetes mellitus: a real-world observational study. *Diabetologia*. 2019 Apr;62(4):621-632. doi: 10.1007/s00125-018-4806-9.
7. Morieri ML, Consoli A, Sesti G, Purrello F, Avogaro A, Fadini GP, et al. Comparative effectiveness of dapagliflozin vs DPP -4 inhibitors on a composite endpoint of HbA1c, body weight and blood pressure reduction in the real world. *Diabetes Metab Res Rev*. 2021;37(1):e3353. doi: 10.1002/dmrr.3353.
8. Hamid A, Vaduganathan M, Oshunbade AA, Ayyalasomayajula KK, Kalogeropoulos AP, Lien LF, et al. Antihyperglycemic Therapies With Expansions of US Food and Drug Administration Indications to Reduce Cardiovascular Events: Prescribing Patterns Within an Academic Medical Center. *J Cardiovasc Pharmacol*. 2020;76(3):313-320. doi: 10.1097/FJC.0000000000000864.
9. Scherthaner G, Shehadeh N, Ametov AS, Bazarova AV, Ebrahimi F, Fasching P, et al. Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. *Cardiovasc Diabetol* 2020;19(1):185. doi:10.1186/s12933-020-01154-w.
10. McCoy RG, Dykhoff HJ, Sangaralingham L, Ross JS, Karaca-Mandic P, Montori VM, et al. Adoption of New Glucose-Lowering Medications in the U.S.-The Case of SGLT2i: Nationwide Cohort Study. *Diabetes Technol Ther*. 2019;21(12):702-712. doi: 10.1089/dia.2019.0213.
11. Kim SH, Chang TI, Mahaffey KW. A Call for a New Paradigm for Diabetes Care in the Era of Sodium Glucose Cotransporter-2 Inhibitors (SGLT2i's). *Cardiol Ther*. 2020;9(2):219-225. doi: 10.1007/s40119-020-00190-7.
12. Kozakova M and Palombo C. Diabetes Mellitus, Arterial Wall, and Cardiovascular Risk Assessment. *Int J Environ Res Public Health*. 2016;13(2):201. doi: 10.3390/ijerph13020201.
13. Prenner SB and Chirinos JA. Arterial stiffness in diabetes mellitus. *Atherosclerosis*. 2015;238(2):370-379. doi: 10.1016/j.atherosclerosis.2014.12.023.
14. Chirinos JA, Segers P, Hughes T, Townsend R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74(9):1237-1263. doi: 10.1016/j.jacc.2019.07.012.
15. Patoulias D, Papadopoulos C, Stavropoulos K, Zografou I, Doumas M, Karagiannis A. Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: The potential role of sodium-glucose co-transporter-2 inhibitors. *J Clin Hypertens (Greenwich)*. 2020;22(4):562-571. doi: 10.1111/jch.13831.
16. Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. *Cardiovasc Diabetol*. 2017;16(1):138. doi: 10.1186/s12933-017-0621-8.
17. Hidalgo Santiago JC, Maraver Delgado J, Cayón Blanco M, López Saez JB, Gómez-Fernández P. Effect of dapagliflozin on arterial stiffness in patients with type 2 diabetes mellitus. *Med Clin (Barc)*. 2020;154(5):171-174. doi: 10.1016/j.medcli.2019.05.028.
18. Hong J-Y, Park K-Y, Kim J-D, Hwang W-M, Lim D-M. Effects of 6 Months of Dapagliflozin Treatment on Metabolic Profile and Endothelial Cell Dysfunction for Obese Type 2 Diabetes Mellitus Patients without Atherosclerotic Cardiovascular Disease. *J Obes Metab Syndr*. 2020;29(3):215-221. doi: 10.7570/jomes20040.
19. Smulyan H, Lieber A, Safar ME. Hypertension, Diabetes Type II, and Their Association: Role of Arterial Stiffness. *Am J Hypertens*. 2016;29(1):5-13. doi: 10.1093/ajh/hpv107.
20. Petrykiv S, Sjöström CD, Greasley PJ, Xu J, Persson F, Heerspink HJL. Differential Effects of Dapagliflozin on Cardiovascular Risk Factors at Varying Degrees of Renal Function. *Clin J Am Soc Nephrol*. 2017;12(5):751-759. doi: 10.2215/CJN.10180916.
21. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347-357. doi: 10.1056/NEJMoa1812389.
22. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.
23. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. A trial to evaluate the effect of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail*. 2019;21(5):665-675. doi: 10.1002/ejhf.1432.
24. Del Prato S, Nauck M, Durán-García S, Maffei L, Rohwedder K, Theuerkauf A, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. *Diabetes Obes Metab*. 2015;17(6):581-590. doi: 10.1111/dom.12459.
25. Szekeres Z, Toth K, Szabados E. The Effects of SGLT2 Inhibitors on Lipid Metabolism. *Metabolites*. 2021;11(2):87. doi: 10.3390/metabo11020087.

26. Calapkulu M, Cander S, Gul OO, Ersoy C. Lipid profile in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective lipid profile from single center. *Diabetes Metab Syndr*.2019;13(2):1031-1034.doi: 10.1016/j.dsx.2019.01.016.
27. Mazidi M, Rezaie P, Gao H-K, Kengne AP. Effect of Sodium-Glucose Cotransport-2 Inhibitors on Blood Pressure in People With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of 43 Randomized Control Trials With 22 528 Patients. *J Am Heart Assoc* 2017;6(6):e004007. doi:10.1161/JAHA.116.004007.
28. Jabbour SA, Frías JP, Guja C, Hardy E, Ahmed A, Öhman P, et al. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly, or dapagliflozin, added to metformin monotherapy, on body weight, systolic blood pressure, and triglycerides in patients with type 2 diabetes in the DURATION-8 study. *Diabetes Obes Metab* 2018;20(6):1520-1525. doi: 10.1111/dom.13296.
29. Chen M-B, Wang H, Cui W-Y, Xu H-L, Zheng Q-H. Effect of SGLT inhibitors on weight and lipid metabolism at 24weeks of treatment in patients with diabetes mellitus: A systematic review and network meta-analysis. *Medicine (Baltimore)*. 2021;100(6):e24593.doi: 10.1097/MD.00000000000024593.
30. Cha S-A, Park Y-M, Yun J-S, Lim T-S, Song K-H, Yoo K-D, et al. A comparison of effects of DPP-4 inhibitor and SGLT2 inhibitor on lipid profile in patients with type 2 diabetes. *Lipids Health Dis* 2017;16(1):58. doi:10.1186/s12944-017-0443-4.
31. Fadini GP, Bonora BM, Zatti G, Vitturi N, Iori E, Marescotti MC, et al. Effects of the SGLT2 inhibitor dapagliflozin on HDL cholesterol, particle size, and cholesterol efflux capacity in patients with type 2 diabetes: a randomized placebo-controlled trial. *Cardiovasc Diabetol* 2017;16(1):42. doi:10.1186/s12933-017-0529-3.
32. Hayashi T, Fukui T, Nakanishi N, Yamamoto S, Tomoyasu M, Osamura A, et al. Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: comparison with sitagliptin. *Cardiovasc Diabetol* 2017;16(1):8. doi:10.1186/s12933-016-0491-5.
33. Imre E, Gunhan HG, Erel P, Ustay O. SGLT2 inhibitors improve plasma atherogenic biomarkers in patients with type 2 diabetes: a real world retrospective observational study. *Minerva Endocrinol (Torino)* 2021. doi:10.23736/S2724-6507.21.03465-5.
34. Rosenstock J, Mathieu C, Chen H, Garcia-Sanchez R, Saraiva GL. Dapagliflozin versus saxagliptin as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin. *Arch Endocrinol Metab* 2018;62(4):424-430. doi:10.20945/2359-3997000000056.
35. Sanz-Serra P, Pedro-Botet J, Flores-Le Roux JA, Benaiges D, Chillarón JJ. Dapagliflozina: Más allá del control glucémico en el tratamiento de la diabetes mellitus tipo 2. *Clínica e Investigación en Arteriosclerosis* 2015;27(4):205-211. doi:10.1016/j.arteri.2014.11.001.
36. Fioretto P, Mansfield TA, Ptaszynska A, Yavin Y, Johnsson E, Parikh S. Long-Term Safety of Dapagliflozin in Older Patients with Type 2 Diabetes Mellitus: A Pooled Analysis of Phase IIb/III Studies. *Drugs Aging* 2016;33(7):511-522. doi:10.1007/s40266-016-0382-1.
37. Tsapas A, Avgerinos I, Karagiannis T, Malandris K, Manolopoulos A, Andreadis P, et al. Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis. *Ann Intern Med* 2020;173(4):278-286. doi:10.7326/M20-0864.
38. Feng M, Lv H, Xu X, Wang J, Lyu W, Fu S. Efficacy and safety of dapagliflozin as monotherapy in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2019;98(30):e16575. doi:10.1097/MD.00000000000016575.
39. Henry RR, Strange P, Zhou R, Pettus J, Shi L, Zhuplatov SB, et al. Effects of Dapagliflozin on 24-Hour Glycemic Control in Patients with Type 2 Diabetes: A Randomized Controlled Trial. *Diabetes Technol Ther* 2018;20(11):715-724. doi:10.1089/dia.2018.0052.
40. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab* 2012;97(3):1020-1031. doi:10.1210/jc.2011-2260.
41. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019;21(6):1291-1298. doi:10.1111/dom.13670.
42. Furtado RHM, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. *Circulation* 2019;139(22):2516-2527. doi:10.1161/CIRCULATIONAHA.119.039996.
43. Persson F, Nyström T, Jørgensen ME, Carstensen B, Gulseth HL, Thuresson M, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes ( CVD-REAL Nordic ) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study. *Diabetes Obes Metab* 2018;20(2):344-351.doi:10.1111/dom.13077.
44. Filion KB, Lix LM, Yu OH, Dell’Aniello S, Douros A, Shah BR, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. *BMJ* 2020;370:m3342. doi:10.1136/bmj.m3342.

45. Kohsaka S, Lam CSP, Kim DJ, Cavender MA, Norhammar A, Jørgensen ME, et al. Risk of cardiovascular events and death associated with initiation of SGLT2 inhibitors compared with DPP-4 inhibitors: an analysis from the CVD-REAL 2 multinational cohort study. *Lancet Diabetes Endocrinol* 2020;8(7):606-615. doi:10.1016/S2213-8587(20)30130-3.
46. Kosiborod M, Birkeland KI, Cavender MA, Fu AZ, Wilding JP, Khunti K, et al. Rates of myocardial infarction and stroke in patients initiating treatment with SGLT2-inhibitors versus other glucose-lowering agents in real-world clinical practice: Results from the CVD-REAL study. *Diabetes Obes Metab* 2018;20(8):1983-1987. doi:10.1111/dom.13299.
47. Li C-X, Liang S, Gao L, Liu H. 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. doi:10.1371/journal.pone.0244689.
48. Dicembrini I, Tomberli B, Nreu B, Baldereschi GI, Fanelli F, Mannucci E, et al. Peripheral artery disease and amputations with Sodium-Glucose co-Transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*. 2019;153:138-144. doi:10.1016/j.diabres.2019.05.028.
49. Heyward J, Mansour O, Olson L, Singh S, Alexander GC. Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: A systematic review and meta-analysis. *PLoS One* 2020;15(6):e0234065. doi:10.1371/journal.pone.0234065.
50. Bonaca MP, Wiviott SD, Zelniker TA, Mosenzon O, Bhatt DL, Leiter LA, et al. Dapagliflozin and Cardiac, Kidney, and Limb Outcomes in Patients With and Without Peripheral Artery Disease in DECLARE-TIMI 58. *Circulation* 2020;142(8):734-747. doi:10.1161/CIRCULATIONAHA.119.044775.
51. Lee H-F, Chen S-W, Liu J-R, Li P-R, Wu L-S, Chang S-H, et al. Major adverse cardiovascular and limb events in patients with diabetes and concomitant peripheral artery disease treated with sodium glucose cotransporter 2 inhibitor versus dipeptidyl peptidase-4 inhibitor. *Cardiovasc Diabetol* 2020;19(1):160. doi:10.1186/s12933-020-01118-0.
52. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. *Cardiovasc Diabetol*. 2016;15:37. doi:10.1186/s12933-016-0356-y.
53. Al Hamed FA and Elewa H. Potential Therapeutic Effects of Sodium Glucose-linked Cotransporter 2 Inhibitors in Stroke. *Clin Ther* 2020;42(11):e242-e249. doi:10.1016/j.clinthera.2020.09.008.
54. American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2021. *Diabetes Care*. 2021;44(Suppl 1):S125-S150.doi: 10.2337/dc21-S010.
55. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* 2019;139(22):2528-2536. doi:10.1161/CIRCULATIONAHA.119.040130.
56. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). *Eur Heart J*.2020;41(36):3402-3418. doi:10.1093/eurheartj/ehaa496.
57. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, et al. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. *Circulation* 2020;141(2):90-99. doi:10.1161/CIRCULATIONAHA.119.044138.
58. McEwan P, Darlington O, McMurray JJV, Jhund PS, Docherty KF, Böhm M, et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *Eur J Heart Fail* 2020;22(11):2147-2156. doi:10.1002/ehfj.1978.
59. Cai R-P, Xu Y-L, Su Q. Dapagliflozin in Patients with Chronic Heart Failure: A Systematic Review and Meta-Analysis. *Cardiol Res Pract* 2021;2021:6657380. doi:10.1155/2021/6657380.
60. McMurray JJV, Wheeler DC, Stefánsson BV, Jongs N, Postmus D, Correa-Rotter R, et al. Effect of Dapagliflozin on Clinical Outcomes in Patients With Chronic Kidney Disease, With and Without Cardiovascular Disease. *Circulation*. 2021;143(5):438-448. doi:10.1161/CIRCULATIONAHA.120.051675.
61. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation*.2017;136(3):249-259. doi:10.1161/CIRCULATIONAHA.117.029190.
62. Norhammar A, Bodegård J, Nyström T, Thuresson M, Nathanson D, Eriksson JW. Dapagliflozin and cardiovascular mortality and disease outcomes in a population with type 2 diabetes similar to that of the DECLARE-TIMI 58 trial: A nationwide observational study. *Diabetes Obes Metab* 2019;21(5):1136-1145. doi:10.1111/dom.13627.
63. Cox ZL, Collins SP, Aaron M, Hernandez GA, Iii ATM, Davidson BT, et al. Efficacy and safety of dapagliflozin in acute heart failure: Rationale and design of the DICTATE-AHF trial. *Am Heart J*. 2021;232:116-124. doi:10.1016/j.ahj.2020.10.071.

64. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kossiorod MN, et al. Dapagliflozin in Heart Failure with Preserved and Mildly Reduced Ejection Fraction: Rationale and Design of the DELIVER Trial. *Eur J Heart Fail.* 2021;23(7):1217-1225. doi: 10.1002/ejhf.2249.
65. Writing Committee, Maddox TM, Januzzi JL, Allen LA, Breathett K, Butler J, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;77(6):772-810. doi:10.1016/j.jacc.2020.11.022.
66. Seferović PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, et al. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur J Heart Fail.* 2020;22(2):196-213. doi:10.1002/ejhf.1673.
67. Khunti K, Gomes MB, Pocock S, Shestakova MV, Pintat S, Fenici P, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: A systematic review. *Diabetes Obes Metab.* 2018;20(2):427-437. doi:10.1111/dom.13088.
68. Mata-Cases M, Franch-Nadal J, Real J, Vlachos B, Gómez-García A, Mauricio D. Evaluation of clinical and antidiabetic treatment characteristics of different sub-groups of patients with type 2 diabetes: Data from a Mediterranean population database. *Prim Care Diabetes.* 2021;15(3):588-595. doi:10.1016/j.pcd.2021.02.003.
69. Khan MS, Butler J, Greene SJ. The Time Is Now for Sodium Glucose Co-Transporter 2 Inhibitors for Heart Failure: A Call to Overcome Clinical Inertia. *Circ Heart Fail.* 2020;13(12):e008030. doi:10.1161/CIRCHEARTFAILURE.120.008030.
70. Greiver M, Havard A, Bowles JK, Kalia S, Chen T, Aliarzadeh B, et al. Trends in diabetes medication use in Australia, Canada, England, and Scotland: a repeated cross-sectional analysis in primary care. *Br J Gen Pract.* 2021;71(704):e209-e218. doi:10.3399/bjgp20X714089.
71. Chahine Nicole and Al-Kindi Sadeer. Under-prescription of sgl2 inhibitors in patients with diabetes and cardiovascular disease in the united states. *J Am Coll Cardiol.* 2020 Mar; 75 (11\_Supplement\_1) 1915 doi:10.1016/S0735-1097(20)32542-0.
72. Lam D and Shaikh A. Real-Life Prescribing of SGLT2 Inhibitors: How to Handle the Other Medications, Including Glucose-Lowering Drugs and Diuretics. *Kidney360.* 2021;2(4):742-746. doi:10.34067/KID.0000412021.
73. Gorgojo-Martínez JJ. New glucose-lowering drugs for reducing cardiovascular risk in patients with type 2 diabetes mellitus. *Hipertens Riesgo Vasc.* 2019;36(3):145-161. doi:10.1016/j.hipert.2019.03.005.