EXPERT OPINION / UZMAN GÖRÜŞÜ

Sodium glucose co-transporter 2 inhibitors in heart failure therapy

Kalp yetersizliği tedavisinde sodyum glikoz ko-transporter 2 inhibitörleri

Yüksel Çavuşoğlu, M.D.,[1] Hakan Altay, M.D.,[2] Avivit Cahn, M.D.,[3] Ahmet Çelik, M.D.,[4] Şerafettin Demir, M.D.,[5] Barış Kılıçaslan, M.D.,[6] Sanem Nalbantgil, M.D.,[7] Itamar Raz, M.D.,[3] Ahmet Temizhan, M.D.,[8] Özlem Yıldırımtürk, M.D.,[9] Mehmet Birhan Yılmaz, M.D.[10]

[1]Department of Cardiology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey
[2]Department of Cardiology, Başkent University Faculty of Medicine, İstanbul, Turkey
[3]Hadassah Hebrew University Hospital, Jerusalem, Israel
[4]Department of Cardiology, Mersin University Faculty of Medicine, Mersin, Turkey
[5]Department of Cardiology, Adana City Training and Research Hospital, Adana, Turkey
[6]Department of Cardiology, University of Health Sciences İzmir Tepecik Training and Research Hospital, İzmir, Turkey
[7]Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey
[8]Department of Cardiology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey
[9]Department of Cardiology, Health Sciences University Dr. Siyami Ersek Thoracic & Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[10]Department of Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are a new class of drugs for patients with type 2 diabetes (T2DM) which inhibit urinary glucose reabsorption in the proximal tubule of the nephron and result in glucosuria, natriuresis and diuresis. In large, randomized clinical trials, SGLT-2i have been shown to reduce major cardiovascular (CV) events and heart failure (HF) hospitalizations in patients with T2DM who have atherosclerotic CV disease or CV risk factors. In these trials, SGLT-2i is have their greatest and most consistent effect on reducing the risk of HF hospitalization. The reduction in HF hospitalization was also observed in subgroups of patients with a HF diagnosis at baseline, which raised the possibility of a clinical benefit of SGLT-2i in HF patients, regardless of the presence or absence of T2DM. In very recently published DAPA-HF trial, a SGLT-2i, dapagliflozin treatment on top of standard HF therapy has been shown to have clear clinical benefits in terms of reducing HF hospitalization, CV mortality, all-cause mortality and improving quality of life in HF patients. This compelling evidence suggests that SGLT-2i have a potential to be an effective treatment option in HF, regardless of diabetes. This article provides a comprehensive overview focused on the role of SGLT-2i in the treatment of HF.

ÖZET

Sodyum glikoz ko-transporter-2 inhibitörleri (SGLT-2i), glükoz geri emiliminin sağlandığı böbrek proksimal tübüllerinde glikoz reabsorbsiyonunu engelleyip glükozuri, diürez ve natriüreze neden olarak etkili olan yeni antidiyabetik ajanlardır. Geniş çaplı randomize klinik çalışmalarda, aterosklerotik kardiyovasküler (KV) hastalığı veya yüksek KV risk faktörleri olan tip 2 diyabette (T2DM), majör KV olayları ve kalp yetersizliğine (KY) bağlı hastane yatışlarını azalttığı ortaya konmuştur. Bu çalışmalarda en büyük ve tutarlı etkinin KY nedenli hastane yatışlarını azaltması üzerine olduğu gözlenmiştir. KY nedenli hastane yatışlarına etkisinin KY tanısı bulunan hasta subgruplarında da gösterilmiş olması SGLT-2i'lerin T2DM olsun olmasın tüm KY olgularında klinik yararlar sağlayabileceği düşüncesini ortaya koymuştur. Yeni yayınlanan DAPA-HF çalışmasında, standart KY tedavisi üzerine eklenen ve SGLT-2i olan dapagliflozinin diyabet olsun olmasın KY bulunan olgularda KY nedenli hastane yatışlarını, KV mortalite ve tüm nedenli mortaliteyi azalttığı, yaşam kalitesini düzelttiği gösterilmiştir. Bu sonuçlar SGLT-2i'lerin KY'de etkin bir tedavi seçeneği olma potansiyeline sahip olduğunu desteklemektedir. Bu derlemede SGLT-2i'lerin KY tedavisindeki rolü değerlendirilmektedir.

Received: February 27, 2020 *Accepted:* February 28, 2020

Correspondence: Dr. Yüksel Çavuşoğlu. Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Eskişehir, Turkey.
Tel: +90 222 - 239 29 79 e-mail: yukselc@ogu.edu.tr

Introduction

Yüksel Çavuşoğlu

Sodium glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) are antidiabetic agents that act by interfering with glucose reabsorption in renal proximal tubules, where glucose is mainly reabsorbed. SGLT-2 inhibitors have been shown to reduce hospitalizations for heart failure (HF) in patients type 2 diabetes mellitus (T2DM) and established atherosclerotic cardiovascular (CV) disease (ASCVD) or high CV risk factors , focusing particular interest on these drugs.[1–3] These agents increase urinary glucose excretion as well as sodium excretion. Fluid excretion increases together with osmotic diuresis and natriuresis. Thus, these drugs cause a decrease in extravascular and intravascular volume, similar to the effect of a diuretic. They also reduce blood pressure and body weight. Unlike diuretics, these agents have no negative effects on renal function, and they have been reported to significantly imrove the outcomes related to renal clinical deterioration. These favorable effects suggest that SGLT-2 inhibitors have the potential to offer an effective treatment option in HF independent of diabetes. The fact that these agents have been shown to reduce hospitalization for HF across all studies in patients with T2DM and ASCVD, and the similar outcomes observed in HF subgroup analyses indicate that the clinical benefits of SGLT-2 inhibitors may also be applicable in patients with HF.[1–3] Recent results from the DAPA-HF[4] and DEFINE-HF[5] studies have demonstrated the clinical benefit of SGLT-2 inhibitors added to standard HF treatment in patients with HF independent of diabetes, bringing a brand new approach to HF treatment.

Mechanism of Action of SGLT-2 Inhibitors in Heart Failure

Mehmet Birhan Yılmaz

The SGLT-2 and SGLT-1 system in renal proximal tubules are responsible for glucose reabsorption, with approximately 90% of glucose reabsorption occurring through a SGLT-2-mediated pathway and 10% via SGLT-1 in proximal tubules. SGLT-2 inhibitors interfere with glucose reabsorption, thereby leading to glycosuria as well as natriuresis and diuresis. Upon demonstration of the favorable CV benefits of SGLT-2 inhibitors, there have been increasing remarks that this class of drugs may in fact be more than simply glycosuric antidiabetics. The vast majority of these remarks rely on additional results from large trials studying these agents as antidiabetics and the pathophysiological mechanism based on the effects at receptor level while an important proportion of the opinions stem from animal experiments (Fig. 1); however, these have not been demonstrated as a whole to date. Nevertheless, there is an increased interest in this drug class among physicians involved in HF treatment.

Natriuretic and diuretic effect

SGLT-2 inhibitors may positively improve ventricular load by reducing preload through natriuretic and diuretic effects. Apart from natriuresis and glycosuria, dapagliflozin has also been shown to reduce tissue sodium levels in T2DM patients.[6] This effect is thought to occur as the excretion of sodium, which escapes from the systemic effect and accumulates among glycosaminoglycans. These effects ultimately lead to volume contraction, i.e. hemoconcentration or, in other words, increased hematocrit levels. For instance, the CV benefit was largely associated with this effect in the empagliflozin study.[7]

SGLT-2 inhibitors may cause volume contraction by directly reducing interstitial fluid, contrary to other diuretics that reduce intravascular fluid more prominently, thereby indirectly affecting the interstitial region. For example, dapagliflozin was shown to differ from other diuretics by its mode of action.[8] However, this has not been fully proven to date and there may be other mechanisms responsible for the positive effect not observed with conventional diuretics.[9] In clinical trials, gliflozins have been shown to cause weight loss (up to 3 kilograms with long-term treatment) and a slight

Kısaltmalar:

ACEI	*Angiotensin converting enzyme inhibitor*
ARB	*Angiotensin II receptor blocker*
ASCVD	*Atherosclerotic cardiovascular disease*
ATP	*Adenosine triphosphate*
CI	*Confidence interval*
rEF	*Reduced ejection fraction*
GFR	*Glomerular filtration rate*
HR	*Hazard ratio*
CKD	*Chronic kidney disease*
KCCQ	*The Kansas City Cardiomyopathy Questionnaire*
pEF	*Preserved ejection fraction*
CV	*Cardiovascular*
HF	*Heart failure*
MI	*Myocardial infarction*
NHE	*Na-H exchanger 1*
NYHA	*New York Heart Association*
ESRD	*End-stage renal disease*
SGLT-2i	*Sodium glucose co-transporter-2 inhibitors*
T2DM	*Type 2 diabetes mellitus*
UACR	*Urinary albumin/creatinine ratio*

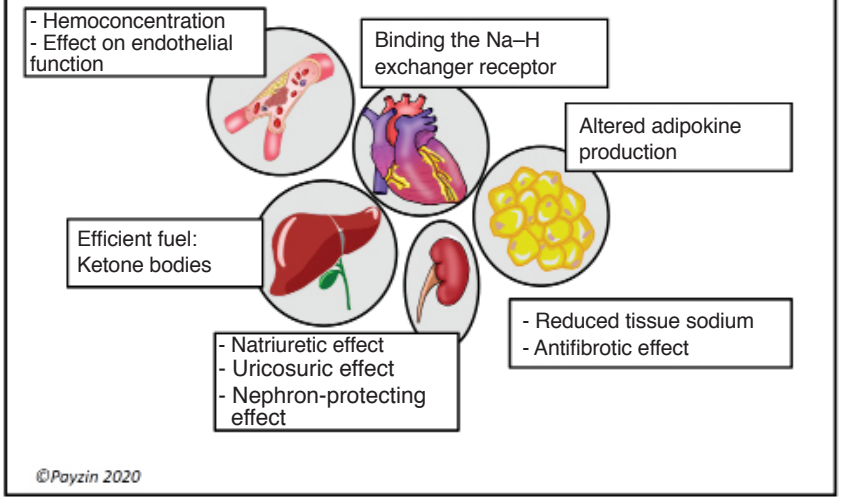

Figure 1. Potential effects of gliflozins in heart failure.

decrease in blood pressure due to urinary glucose and sodium excretion.[10,11] The minimum treatment duration required to achieve the full effect has been reported as six months.[12] However, there is no clear data showing HF-specific benefits from these effects deemed to be favorable in CV terms.

Still, SGLT-2 inhibitors have a unique position among the diuretics used in clinical setting as they regulate proximal tubule functions. Furthermore, this natriuretic response is important in terms of tubuloglomerular feedback and vasoconstriction in afferent arterioles.[13] as intraglomerular pressure is ultimately reduced and protective effects are observed at nephron level, which have also been shown in clinical trials.[14]

Direct effect on myocardium

There is substantial evidence indicating that SGLT-2 inhibitors bind and inhibit the Na-H exchanger 1 (NHE) in myocardium.[15,16] Another isoform of this receptor is expressed in kidneys and responsible for tubular sodium reabsorption. There are signs indicating that gliflozins inhibit this receptor as well.[17] Inhibition of NHE, known to increase cytosolic sodium and calcium in experimental HF models, may be beneficial through a number of pathways. At least one of these may be related to improved mitochondrial function in the presence of insulin resistance.[18] Another pathway leading to a direct myocardial effect may be the decrease in cardiac fibrosis. Empagliflozin has been shown to reduce cardiac fibrosis and oxidative stress in a diabetic mouse model.[19] Confirmation of this favorable effect in ongoing clinical trials may render gliflozins as the strongest choice for evidence-based medicine in HF with preserved ejection fraction (HFpEF).

Efficient fuel hypothesis

Gliflozins are known to increase the production of ketone bodies, i.e. beta-hydroxybutyrate, acetoacetate and acetone by increasing glucagon levels and lowering insulin levels, thereby altering the insulin/glucagon ratio.[20] Therefore, it appears possible to mimic a ketogenic diet with these drugs and even to potentiate this effect. Ketone bodies offer an alternative and more efficient fuel. While 100 g glucose provides 8.7 kg adenine triphosphate (ATP), 100 g beta-hydroxybutyrate can produce 10.5 kg ATP and 100 g acetoacetate can produce 9.4 kg ATP.[21] This efficiency may be of critical importance in conditions such as HF.[22,23] In a doxorubicin-induced HF animal model, the cardioprotective effect was associated with increased beta-hydroxybutyrate levels.[24] This effect is also associated with the direct myocardial effect.

Other possible effects

In an animal model, dapagliflozin administered during daytime was shown to decrease adipokine levels and adipocyte size as well as plasma glucose levels.[25] Moreover, in adipocyte tissues obtained from patients undergoing open heart surgery, dapagliflozin was shown to reduce the release of pro-inflammatory chemokines and positively affect the differentiation of epicardial adipocytes.[26]

In an experimental animal model, acute dapagliflozin administration was shown to increase endothelium-dependent vasodilation in a dose-dependent manner while chronic administration improved endothelial function by reducing vascular adhesion molecules and vascular wall infiltration *in vivo*.[27] On the other hand, the ADDENDA-BHS2 study currently investigates the effect of dapagliflozin on flow-related vasodilation in patients with diabetic endothelial dysfunction.[28]

In conclusion, gliflozins provide a strong candidate for widespread use in all phenotypes of HF syndrome with their effects listed here or those that have not been elucidated to date. Currently, within the scope of evidence-based medicine, these agents have become a main leaf of a four-leaf clover in the treatment of HF with reduced ejection fraction (HFrEF).

Studies on SGLT-2 Inhibitors from Diabetes to Heart Failure

Yüksel Çavuşoğlu

The first study to evaluate the effect of SGLT-2 inhibitors on CV outcomes in T2DM was the EMPA-REG OUTCOME study.[1] A total of 7,020 T2DM patients with established ASCVD were enrolled in this randomized, double-blind study to compare 10 mg and 25 mg empagliflozin versus placebo in terms CV outcomes. Mean duration of follow-up was 3.1 years. In the study in which the primary hypothesis was non-inferiority, empagliflozin was shown to be non-inferior than placebo at the primary endpoint of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke, and superior than placebo in the superiority analysis [hazard ratio (HR): 0.86, 95% confidence interval (CI), 0.74–0.99, p<0.001 for non-inferiority and p<0.04 for superiority]. Furthermore, there was a 35% decrease in hospitalization for HF alone (HR: 0.65, 95% CI, 0.50–0.85, p=0.002] and a 38% decrease in CV death alone (HR: 0.62; 95% CI, 0.49–0.77; p<0.001) (Table 1).

Subsequently, results came from the randomized, double-blind CANVAS study, which compared canagliflozin 100 mg and 300 mg versus placebo in terms of CV outcomes in 10,142 T2DM patients who had established ASCVD or CV risk factors alone.[2] Mean duration of follow-up was 3.6 years. Similarly, the primary hypothesis was non-inferiority in this study and canagliflozin was found to be non-inferior than placebo at the primary endpoint of CV death, non-fatal MI or non-fatal stroke and superior in the superiority analysis (HR=0.86, 95% CI=0.75–0.97, p<0.001 for non-inferiority and p<0.02 for superiority). In addition, a significant decrease was observed in hospitalization for HF alone (33%; HR=0.67, 95% CI=0.52–0.87) while a non-significant decrease was seen in CV death alone (13%; HR: 0.87; 95% CI, 0.72-1.06) (Table 1).

The DECLARE-TIMI 58 study compared dapagliflozin versus placebo in terms of CV outcomes in 17,160 T2DM patients, including those with established ASCVD as well as subjects with CV risk factors alone.[3] Taking into account the results of the EMPA-REG OUTCOME study, which were published while the study in question was in progress, two primary endpoints (1-MACE: CV death, non-fatal MI or non-fatal stroke; and 2-CV death or hospitalization for HF) were evaluated. Mean duration of follow-up was 4.2 years. The study, in which the primary hypothesis was non-inferiority, showed non-inferiority of dapagliflozin versus placebo (p<0.001) for MACE, although a significant p-value was not observed for superiority. However, a significant decrease was noted in the other primary endpoint consisting of CV death and hospitalization for HF (HR=0.83, 95% CI, 0.73–0.95, p=0.005). Furthermore, hospitalization for HF alone was significantly decreased with dapagliflozin (HR=0.73, 95% CI=0.61–0.88) (Table 1).

A meta-analysis evaluating these 3 large studies which included 34,322 subjects in total[29] reported that SGLT-2 inhibitors reduced CV death or hospitalization for HF by 23% (HR 0.77, 0.71–0.84, p<0.0001) and that this benefit was similar in patients with established ASCVD and those with CV risk factors alone. Similarly, it was concluded that SGLT-2 inhibitors significantly reduced hospitalization for HF alone both in patients with established ASCVD (HR=0.71, 0.61–0.84, p<0.0001) and those with CV risk factors alone (HR=0.79, 0.71–0.88, p<0.0001).[29]

The DAPA-HF study, which was designed based on the hypothesis that SGLT-2 inhibitors would provide clinical benefit in subjects with HF alone as they were shown to significantly and consistently reduce hospitalization for HF across all studies,[4] included 4,744 patients with EF <40% and functional capacity classified as New York Heart Association (NYHA) II-IV with or without DM to evaluate the effectiveness and safety of dapagliflozin compared to placebo added to standard HF treatment.

Table 1. Characteristics and outcomes of large clinical studies with SGLT-2 inhibitors

	EMPA-REG OUTCOME	CANVAS	DECLARE TIMI-58	DAPA-HF
SGLT-2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin
Number of patients	7020	10,142	17,160	4744
Age, years	63.1	63.3	63.9	66.3
Follow-up, years	3.1	2.4	4.2	1.5
Patient group	T2DM	T2DM	T2DM	HF
Presence of HF	10.1% (n=706)	14.4% (n=1461)	10% (n=1724)	100%
Established CVD	100%	65.6% (n=6656)	40.6% (n=6974)	56% (ischemic HF)
GFR (mL/min/1.73 m^2)	>30	>30	>60	>30
Primary endpoint	CV death/MI/stroke	CV death/MI/stroke	1- CV death/MI/stroke 2- CV death/ HF	Hospitalization or emergency visit for hospitalization HF/ CV death
Reduction in primary endpoint	HR: 0.86, 95% CI, 0.74–0.99	HR: 0.86, 95% CI, 0.75–0.97	1- HR: 0.93; 95% CI, 0.84–1.03 2- HR: 0.83, 95% CI, 0.73–0.95	HR: 0.74; 95% CI, 0.65–0.85
Reduction in HF hospitalization	HR: 0.65, 95% CI, 0.50–0.85	HR: 0.67, 95% CI, 0.52–0.87	HR: 0.73, 95% CI, 0.61–0.88	HR: 0.70, 95% CI, 0.59–0.83
Reduction in CV death	HR: 0.62; 95% CI, 0.49–0.77	HR: 0.87; 95% CI, 0.72–1.06	HR: 0.98; 95% CI, 0.82–1.17	HR: 0.82, 95% CI, 0.69–0.98

SGLT-2 inhibitor: Sodium-glucose co-transporter 2 inhibitors; T2DM: Type 2 diabetes mellitus; GFR, glomerular filtration rate; CV: Cardiovascular; HF: Heart failure; MI: Myocardial infarction; CVD: Cardiovascular disease; HR: hazard ratio.

The primary endpoint was emergency visit for HF or hospitalization for HF or CV death. Dapagliflozin was associated with a significant decrease in the primary endpoint (HR=0.74; 95% CI=0.65–0.85; p<0.001) (Table 1). Furthermore, significantly lower rates were observed in hospitalizations for HF alone (HR=0.70, 95% CI=0.59–0.83), CV death alone (HR=0.82, 95% CI=0.69–0.98), all-cause mortality alone (HR=0.83, 95% CI=0.71–0.97) and CV death or hospitalizations for HF (HR=0.75, 95% CI=0.65–0.85).[4]

DEFINE-HF is another recently published study, which evaluated subjects with HF alone.[5] This relatively smaller study with a short follow-up period included 263 HFrEF patients with EF <40% and NYHA II-IV to investigate the changes in NT-proBNP and quality of life with dapagliflozin at the end of 12 weeks. Results of the study showed significant improvements in quality of life and NT-proBNP levels with dapagliflozin.

When characteristics of patient populations and results of the studies are evaluated together, SGLT-2 inhibitors appear to provide further clinic benefits in terms of CV death and all-cause mortality as the CV risk profile increase in patients with T2DM. However, the clinical benefits for HF may be achieved both in patients with low- and high-CV risk profile. Moreover, results from DAPA-HF demonstrated clinical benefits with SGLT-2 inhibitors both in non-diabetic and non-ischemic HF cases. In other words, DAPA-HF data indicate that SGLT-2 inhibitors may be a part of treatment in all patients with HF, whether diabetic or non-diabetic, in addition to their protective role against HF observed with SGLT-2 inhibitors in patients with T2DM.

SGLT-2 Inhibitors in Primary Prevention of Heart Failure

Barış Kılıçaslan

Studies conducted in diabetic patients have explored the effects of SGLT-2 inhibitors in primary prevention of HF and CV disease. The EMPA-REG study, which

was the first of these studies, showed that empagliflozin significantly decreased hospitalizations for HF in patients with T2DM and history of established CV disease (HR=0.65; (0.50–0.85); p=0.002). The effects of empagliflozin doses (10 mg and 20 mg) utilized in the study were found to be similar.[1] In the CANVAS study, which investigated canagliflozin in patients with T2DM and ASCVD or CV risk factors, hospitalizations for HF was a secondary endpoint and appeared to dissociate early in the canagliflozin group, resulting in a significantly lower rate at the end of the study [HR=0.67 (0.52–0.87); p=0.002]. Unlike EMPA-REG, CANVAS enrolled subjects with CV risk factors without ASCVD comprising 35% of the study population and the superiority of canagliflozin in primary prevention of HF was seen to persist in these patients as well.[2] DECLARE, which was conducted in light of these studies, compared dapagliflozin versus placebo in patients with T2DM and ASCVD or high CV risk and demonstrated a significantly lower rate of hospitalizations for HF in the dapagliflozin group [HR=0.73 (0.61–0.88); p=0.002].[3] Patient characteristics differ in terms of CV disease burden across studies and Zelniker et al.[29] published a meta-analysis including three studies to evaluate the effect of this difference on results. This meta-analysis evaluated a total of 35,322 patients. Of these, 60.2% had history of ASCVD and 39.8 had multiple CV risks without history of ASCVD. The meta-analysis revealed a significant decrease in hospitalization for HF by 31% [HR=0.69 (0.61–0.79), p<0.0001] and this decrease was similar both in patients with ASCVD and those with multiple CV risks. The decrease in hospitalizations for HF was evident with or without a diagnosis of HF.

In line with the results of all the aforementioned studies, one may conclude that SGLT-2 inhibitors significantly mitigate HF development in patients with T2DM. Based on the relevant data, current treatment guidelines have recognized SGLT-2 inhibitors for the primary prevention of HF. The use of empagliflozin was firstly recommended with a Class IIa indication to prevent or delay the development of HF in patients with T2DM in the 2016 European HF guidelines.[30] In 2019, European Society of Cardiology and European Foundation for the Study of Diabetes issued guidelines on "Diabetes, Pre-diabetes and Cardiovascular Disease", which included SGLT-2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) as a Class I, evidence level A recommendation to reduce the rate of hospitalizations for HF in T2DM patients.[31] The 2019 Consensus Report on Clinical Practice Updates issued by the European Society of Cardiology Heart Failure Group in 2019 recommended SGLT-2 inhibitors (empagliflozin, canagliflozin or dapagliflozin) to reduce hospitalizations for HF or delay the development of HF in T2DM patients with ASCVD or high risk of CV disease. The consensus in question highlighted the sufficiency of available data to prove the class effect of SGLT-2 inhibitors in reducing hospitalizations for HF.[32] Data from studies conducted to date and the recommendations in guidelines support the efficacy of SGLT-2 inhibitors in the primary prevention of HF in patients with T2DM and established ASCVD or high-risk factors for CV disease.

SGLT-2 Inhibitors in Heart Failure Accompanied by Diabetes

Özlem Yıldırımtürk

Diabetes is not only an independent known risk factor for HF, but also plays a role as an independent risk factor in morbidity and mortality in these patients.[33] About 20–40% of HF patients have concomitant T2DM.[34] The greatest advance in therapeutic management of diabetic HF patients has been the demonstration of reduced hospitalizations for HF with SGLT-2 inhibitors in recent years.[29] The EMPA-REG OUTCOME,[35] CANVAS[36] and DECLARE TIMI-58[3] studies conducted in T2DM patients with established ASCVD or CV risk factors have shown that empagliflozin,[35] canagliflozin and dapagliflozin, respectively, decrease hospitalizations for HF in patients with T2DM. Only 10.1% of the patients enrolled in EMPA-REG OUTCOME had known history of HF as the study mainly included T2DM patients with established ASCVD. In the patient group with T2DM and concomitant HF, outcomes were found to be in favor of empagliflozin in terms of hospitalization for HF/CV death (16.2% vs 20.1%; HR=0.72, 95% CI=0.50–1.04), hospitalization for HF alone (10.4% vs 12.3%; HR=0.75, 95% CI=0.48–1.19) and CV death alone (8.2% vs 11.1%; HR=0.79, 95% CI=0.52–1.2).[37] In an analysis employing the Health ABC HF risk score with nine variables, an increased rate of hospitalization for HF/CV death was noted with increasing risk scores in patients on placebo. CV death/hospitalization for HF appeared to be reduced with empagliflozin at all risk levels in patients without underlying HF.

CANVAS and CANVAS-R were combined as the CANVAS program in order to focus on the effects of canagliflozin. While 65.6% of the T2DM patients with high CV risk included in the study had history of established ASCVD, only 14.4% had HF.[36] Evaluation of HF patients revealed outcomes in favor of canagliflozin for CV death/hospitalization for HF [35.4 vs 56.8 per 1000 patient-years, HR=0.61 (95% CI=0.46–0.80), p=0.02], CV death [24.3 vs 31.6 per 1000 patient-years, HR=0.72 (95% CI=0.51–1.02), p=0.17] and hospitalization for HF [14.1 vs 28.1 per 1000 patient-years, HR=0.51 (95% CI=0.33–0.78), p=0.47]. The 5-year evaluation of the net risk showed a significant risk reduction with canagliflozin in rates of CV death/hospitalization for HF (p=0.003) and hospitalization for HF (p=0.01).[38]

Similarly, the DECLARE study, which was conducted at the request of the Food and Drug Administration (FDA) due to safety data, investigated dapagliflozin in high-risk T2DM patients with established ASCVD and CV risk factors. To date, DECLARE-TIMI-58 remains the only study that recorded the patients' EF values. EF was <45% in 3.9% of the patients included in the study and HF diagnosis was established by the physician regardless of EF in 7.7% of the patients.[6] A significant decrease was observed in CV death/hospitalization for HF with dapagliflozin in HFrEF patients compared to those without HFrEF (HR=0.62, 95% CI=0.45-0.86 vs HR=0.88, 95% CI=0.76-1.02, p=0.046). Similarly, dapagliflozin showed significant benefit in terms of all-cause mortality in HFrEF patients (HR=0.59, 95% CI=0.40–0.88, p=0.01) compared to others (HR=0.97, 95% CI=0.86–1.10, p-interaction 0.016).[39]

Since the data of HF patients were based on subgroup analyses in these three studies, more detailed data were deemed necessary in order to investigate the benefit of SGLT-2 inhibitors in T2DM patients. The meta-analysis evaluating these studies together reported significantly reduced risks of CV death/hospitalization for HF (HR=0.71, 95% CI=0.61–0.84), hospitalization for HF alone (HR=0.68, 95% CI=0.55–0.83) and all-cause mortality (HR=0.80, 95% CI=0.67–0.95) with SGLT-2 inhibitors in patients with HF at baseline.[3] Based on these results, specific studies investigating the effectiveness and safety of SGLT-2 inhibitors in HF have been commenced. These include[33] DAPA-HF,[34] EMPEROR-Reduced,[29] EMPEROR-Preserved,[35] DELIVER and,[36] SOLOIST-WHF. While results from EMPEROR-Reduced and EMPEROR-Preserved are expected to be announced in the near future, patient enrollment is expected to be completed in 2021 for DELIVER, which aims to investigate dapagliflozin in HFpEF. The T2DM subgroup analyses of these studies are expected to provide more definitive information concerning the effectiveness of SGLT-2 inhibitors in HF accompanied by diabetes.

DAPA-HF was the first study with published results in the heart failure patient population. In DAPA-HF, 4744 NYHA II-IV patients with EF <40% were randomized to dapagliflozin 10 mg or placebo.[40] The study population consisted 41.8% patients with DM. Primary endpoints (worsening HF or CV-related death) was found to be significantly low with dapagliflozin both in diabetic patients (HR=0.75, 95% CI=0.63–0.90) and those without diabetes (HR=0.73, 95% CI, 0.6–0.88). In the diabetic patients group, significant improvement was achieved with dapagliflozin in the endpoints of hospitalization for HF alone (HR=0.77, 95% CI=0.63–0.94), CV death/hospitalization for HF (HR=0.75, 95% CI=0.63–0.90) and all-cause mortality (HR=0.78, 95% CI=0.63–0.97). One of the important observations in this study was the early dissociation of the curves after treatment initiation and the efficacy of dapagliflozin being independent of the patients' glycemic status. Furthermore, 94% of the patients were receiving an angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) or ARNI, 96% were on a beta-blocker and 71% were receiving a mineralocorticoid receptor antagonist, and the clinical benefit seen with the addition of dapagliflozin to optimal standard of care was significant. Results of the present study (Table 2) indicate that SGLT-2 inhibitors may be a complementary treatment option in the current management of HF in patients with T2DM.

SGLT-2 Inhibitors in Heart Failure with Reduced Ejection Fraction

Hakan Altay

In primary prevention studies (EMPAREG OUTCOME, CANVAS, DECLARE TIMI-58), despite the positive results in terms of preventing HF development and guideline recommendations,[1,2,30,39] it remained unclear whether SGLT-2 inhibitors actually preven-

Table 2. Endpoints of hospitalization for HF in HF patients with T2DM in SGLT-2 inhibitors studies

	Hospitalization for HF					
	Patients		Events per 1000 patient-years		HR	95% CI
	Tedavi	Plasebo	Tedavi	Plasebo		
Patients with underlying heart failure						
EMPA-REG	126	95	2.7	14.5	0.65	0.50–0.85
DECLARE	852	872	10.2	13.1	0.73	0.55–0.96
CANVAS	803	658	14.1	28.1	0.51	0.33–0.78
DAPA-HF	2373	2371	6.9	9.8	0.70	0.59–0.83
Patients without underlying heart failure						
EMPA-REG	4225	2089	4.4	7.1	0.63	0.51–0.78
DECLARE	7730	7706	1.6	2.2	0.73	0.58–0.92
CANVAS	4992	3689	9.8	9.9	0.79	0.57–1.09

HF: Heart failure; HR: Hazard ratio.

ted HFrEF or HFpEF since the patients' EF values were not recorded. However, it was thought that these agents may be effective in both types of HF. Furthermore, only a minority of the patients in these studies had HF and there is no detailed information on EF , symptom burden or whether the patients with HF were receiving the treatment recommended in guidelines. It is therefore difficult to precisely interpret the efficacy of these drugs in patients with HFrEF, yet subgroup analyses have been conducted to generate a hypothesis in this regard. Roughly 5,000 of the 17,168 patients included in DECLARE-TIMI-58 had EF values. Of these, 3.9% had EF <45% and were defined as HFrEF. The subgroup analysis of these subjects showed that dapagliflozin decreased the endpoint of hospitalization for HF/CV death to a greater extent in patients with HFrEF compared to those without HFrEF (HR=0.62 vs 0.88, p-interaction=0.046). While dapagliflozin reduced hospitalizations for HF both in patients with HFrEF and those without HFrEF, mortality was reduced only in the HFrEF group.[39]

Upon the favorable outcomes observed in subgroup analyses of the large trials, DEFINE HF has been one of the first studies to publish results concerning the effectiveness of SGLT-2 inhibitors in subjects with HFrEF.[5] In this small study conducted at 26 centers in the United States, 263 HFrEF patients with NYHA II-IV and EF <40% were randomized to dapagliflozin or placebo. The DEFINE HF study had two primary endpoints. The first was the change in mean NT-proBNP at the end of 12 weeks, and the second was a 5-point increase in the 'Kansas City Cardiomyopathy' questionnaire (KCCQ) or >20% decrease in NT-proBNP. At the end of 12 weeks, there was no difference in mean NT-proBNP between the two groups (1133 pg/mL vs 1191 pg/mL, p=0.43), whereas the second primary endpoint of a 5-point increase in KCCQ or >20% decrease in NT-proBNP was found to be significantly higher proportion of patients in the dapagliflozin group (61.5% vs 50.4%, p=0.043). The DEFINE HF study, which had a short follow-up period, was not designed to investigate hospitalizations for HF and CV death.

DAPA-HF, on the other hand, is the study that aimed to evaluate clinical outcomes in the HFrEF patient population and has published results. In this study, dapagliflozin (10 mg/day) added to standard HF treatment was compared with placebo in 4744 patients with mild-to-moderate HF, i.e. NYHA II-IV and EF <40%.[4] The majority of the patients included in the study were in the NYHA II-III class. Mean follow-up period of the study was 18.2 months. The patients were receiving optimal HFrEF treatment in the background (ACEi 94%, BB 96%, MRA 71%, ARNi 11%). One of the most important aspects of the study was that 55% of the patients included in the study did not have T2DM. The primary endpoint was worsening HF (hospitalization or emergency visit requiring i.v. therapy) or CV death. At the end of the study, SGLT-2 inhibitors

were found to decrease the primary endpoint by 26% (HR=0.74, 95% CI=0.65–0.85). While CV death alone was decreased by 18% (HR=0.82; 95% CI=0.69–0.98), hospitalizations for HF were decreased by 30% (HR=0.70; 95% CI=0.59–0.83). The number needed to treat with dapagliflozin to prevent the development of one of the HF events (hospitalization or emergency visit) was only 16. All-cause mortality was decreased by 17% (HR=0.83, 95% CI=0.71–0.97). The improvement in symptoms measured by KCCQ at the end of eight months was better in favor of dapagliflozin (HR=1.18, 95% CI=1.17–1.21). The safety profile was similar across the two groups. The rates of treatment discontinuation due to adverse events were comparable (4.7% vs. 4.9%). Serious side effects were less common with dapagliflozin (38% vs 42%; p<0.01) and there was no difference in the favorable effect of dapagliflozin on the endpoints in the diabetics group (45%) and those without diabetes (55%). DAPA-HF is important in terms of showing that SGLT-2 inhibitors are beneficial also in HF patients without T2DM while reinforcing the position of SGLT-2 inhibitors in the treatment of T2DM patients with concomitant HFrEF.

There are ongoing studies that investigate the effectiveness of SGLT-2 inhibitors in HFrEF regardless of the presence of T2DM. The currently ongoing SGLT-2 inhibitors studies in HFrEF are shown in Table 3. Results of these studies are expected to consolidate the position of SGLT-2 inhibitors as the fourth drug class after the three main drug classes (ACEi/ARB/ARNI, beta blockers, MRA) used for the treatment of HFrEF.

SGLT-2 Inhibitors in Heart Failure with Preserved Ejection Fraction

Sanem Nalbantgil

Approximately half of the patients with heart failure have HFrEF, and the rest have HF midrange EF or HFpEF. There is no group of drugs identified as agents that prolong survival in HFpEF patients. Diuretic therapy for the treatment of comorbidities and the elimination of congestion are the approaches described in the guidelines. There is increasing evidence that the drug group of SGLT-2 inhibitors, which have been introduced to use in recent years, may have positive effects in these patients.

Table 3. Ongoing clinical studies with SGLT-2 inhibitors in HFrEF

	EMPEROR-REDUCED Empagliflozin (n=3600)	SOLOIST-WHF Sotagliflozin (n=4000)	DETERMINE-REDUCED Dapagliflozin (n=312)	EMPERIAL-REDUCED Empagliflozin (n=312)	EMPIRE-HF Empagliflozin (n=189)
Patient population	-NYHA II-IV, -Patients with high NT-proBNP levels	-Type 2 DM -Emergency visit or hospitalization for HF -Diagnosis of HF(>3 months) -Those receiving a diuretic for >30 days -EF <50% -BNP ≥150; ≥450 if AF is present or NT-proBNP ≥600; ≥1800 pg/mL if AF is present	-NYHA II-IV -LVEF ≤40% -Increased NT-proBNP -6MWD ≥100 and ≤425 m	-6MWD ≤350 m -NYHA II-IV -EF <40% -Increased NT-proBNP	-Receiving optimal HF treatment -LVEF ≤0.40 -eGFR >30 ml/min/1.73 m^2 -BMI <45 kg/m^2 -NYHA I-III
Primary Endpoint	1-CV death 2-Hospitalization for HF	CV death or hospitalization for HF	Change in 6MWD at 16 weeks	Change in 6MWD at 12 weeks	Change in NT-proBNP at 90 days

AF: Atrial fibrillation, BMI: Body mass index; BNP: Brain natriuretic peptide; HFrEF: Heart failure with reduced ejection fraction; DM: Diabetes mellitus; eGFR: Glomerular filtration rate; CV: Cardiovascular; HF: Heart failure; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; 6MWD: 6-minute walking distance.

In the EMPAREG study, which included patients with T2DM and established ASCVD, the rate of HF reported by the investigator was about 10% in the groups receiving placebo or empagliflozin.[1] However, the interpretation of the investigator was taken into consideration for the diagnosis of HF in this study and echocardiographic EF detection or natriuretic peptide values were not available. Data of patients with HFpEF or HFrEF were not evaluated specifically; instead, HF was evaluated in general terms in the study. Hospitalization for HF was decreased significantly by 35% in the group receiving empagliflozin.[1] The rate of reduction in hospitalizations for HF was similar in the groups with and without HF. In addition to hospitalization for HF, significant decrease was observed also in HF-related death, loop diuretic usage (initiation or dose increase), HF reported by the investigator and all-cause hospitalization in the group receiving

Table 4. Ongoing SGLT-2 inhibitors studies in HFpEF

Trial name Clinicaltrials.gov	SGLT-2 inhibitors	Patient population	LVEF	Number of patients	Primary endpoint
DETERMINE-PRESERVED Effects of dapagliflozin on exercise capacity using 6MWD in patients with HFpEF (phase 3)	Dapagliflozin	HFpEF NYHA II-IV	LVEF >40%	400	16 weeks: Change in 6MWD and KCCQ-TSS
Effects of empagliflozin on exercise capacity and left ventricle diastolic function in patients with HFpEF and type 2 DM (phase 4)	Empagliflozin	HFpEF type 2 DM	LVEF >50%	100	24 weeks: Change in 6MWD
DELIVER Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients With Heart Failure With Preserved Ejection Fraction (phase 3)	Dapagliflozin	HFpEF NYHA II-IV	LVEF >40%	4700	-CV death -Hospitalization for HF -Emergency visit/ hospital admission for HF
EMPEROR-PRESERVED Empagliflozin outcome trial in patients with chronic HFpEF (EMPEROR Preserved) (phase 3)	Empagliflozin	HFpEF NYHA II-IV	LVEF >40%	5250	CV death or hospitalization for HF
EMPERIAL PRESERVED Effect of empagliflozin on exercise ability and heart failure symptoms in patients with chronic HFpEF (phase 3)	Empagliflozin	HFpEF	LVEF >40%	300	12 weeks: Change in 6MWD
PRESERVED-HF Dapagliflozin in heart failure with PRESERVED ejection fraction (phase 4)	Dapagliflozin	HFpEF High NP	LVEF ≥45%	320	12 weeks: Change in NP levels

6MWD: 6-minute walking distance; HFpEF: Heart failure with preserved ejection fraction; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire - Total Symptom Score; NP: Natriuretic peptide; NYHA: New York Heart Association.

empagliflozin.[37] There is no analysis to show the rates of HFpEF and HFrEF in patients who developed HF during the follow-up.

In DECLARE, dapagliflozin reduced hospitalizations for HF in the groups with ASCVD or CV risk factors alone in the patient population consisting of those with T2DM and ASCVD or CV risk factors.[3] An analysis of the HF subgroup reported HFrEF (left ventricular EF <45%) in 3.9% of the patients while 7.7% had HFpEF (left ventricular EF >45%) and 88.4% did not have known HF diagnosis at baseline. HFpEF patients were older, female and hypertensive. A subgroup analysis reported that the primary endpoint was decreased more evidently in HFrEF patients while a significant decrease was also observed in patients with HFpEF.[39]

In the CANVAS study,[41] which included 10000 patients with T2DM and ASCVD or CV risk factors, 14.4% of the patients had a diagnosis of HF. Compared to placebo, hospitalization for HF or CV death was significantly decreased in the group receiving canagliflozin. The positive effect of the drug was greater in the group of patients with known HF.[38] In a recently published subgroup analysis of this study, 101 of the patients newly diagnosed with HF were reported to have HFpEF (EF detected by echo >50%), 122 had HFrEF (EF detected by echo <50%) and 61 had HF with unspecified EF. Patients with HFpEF were mostly female and had higher rates of hypertension, obesity and microvascular complications. Compared to placebo, canagliflozin was reported to significantly reduce HF-induced hospitalization similarly in HFpEF patients (HR=0.70; 95% CI=0.55–0.89) and HFrEF patients (HR=0.69; 95% CI=0.48–1.00).[36]

A meta-analysis that included these three studies reported that SGLT-2 inhibitors treatment reduced CV death or HF by 23% and hospitalizations for HF by 31%.[29] This decline was similar in patients with established ASCVD and those with CV risk factors alone. In addition, clinical benefits were similar in patients with pre-study HF and those that developed HF during the study. Apart from clinical outcome studies, there are echocardiography and MRI studies investigating the effects of these drugs on left ventricular mass, remodeling and diastolic functions.[42]

In summary, the available data indicate that the clinical benefits of SGLT-2 inhibitors are similar in both HFrEF and HFpEF patients, in addition to the favorable effects seen on HF in patients with T2DM. Studies investigating the position of SGLT-2 inhibitors in HFpEF patients with and without diabetes are currently ongoing (Table 4). Results of these studies are expected to clarify the role of SGLT-2 inhibitors in HFpEF patients. Nevertheless, the available evidence readily supports that SGLT-2 inhibitors are promising agents in the treatment of HFpEF.

Effect of SGLT-2 Inhibitors on Renal Clinical Outcomes in Heart Failure

Ahmet Temizhan

T2DM is the most important shared denominator and major risk factor responsible for mortality, hospitalization and morbidity associated with ASCVD and renal disease[43,44] In the course of this common pathway, the cardiorenal effects of antidiabetic drugs and glycemic control are considered as the determining factors. The favorable effects observed in CV disease, HF and chronic kidney disease (CKD) with SGLT-2 inhibitors independent of blood sugar lowering effect of these drugs, which are used as antidiabetic agents, has changed the paradigms in T2DM treatment.

Effect of SGLT-2 inhibition on renal clinical outcomes in diabetic patients with CV disease/high CV risk or chronic kidney disease

Prior to CV outcome studies, SGLT-2 inhibitors were shown to improve intraglomerular pressure, proteinuria and glomerular and tubular histopathological damage independent of the blood pressure-lowering effect.[45,46] Clinical studies demonstrated reduced albuminuria and acute but reversible decreases in estimated glomerular filtration rate (eGFR) by 5 mL/min/1.73 m^2 with SGLT-2 inhibitors.[47,49] In fact, long-term outcome studies with SGLT-2 inhibitors showed that the reduced albuminuria and GFR were maintained, with this effect persisting in the long term.[1–3,47,50] While favorable renal effects were seen in all studies, risk reduction appears to be variable. Rate ratio per 1000 patient-years in composite renal outcomes with SGLT-2 inhibition compared to placebo was 47% in DECLARE TIMI-58, 40% in CANVAS and 46% in EMPA-REG OUTCOME, with 30% relative risk reduction observed in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE).[1–3,14] The difference in renal ef-

fects result from the variation in baseline renal function of patients included in studies and the different definitions of renal outcome (Table 5). Cardiorenal events were observed at the lowest rate in DECLARE TIMI-58 and at the highest rate in CREDENCE as patients in DECLARE TIMI-58 had the best renal function at the beginning of treatment while those in CREDENCE had the worst renal function. Again, the highest mean albuminuria was observed in CREDENCE patients.[51]

SGLT-2 inhibition markedly reduced albuminuria in patients with micro- or macroalbuminuria in EMPA-REG OUTCOME, CANVAS and DECLARE TIMI-58 studies.[1–3] In patients with normoalbuminuria at baseline, there was a mild reduction in urinary albumin/creatinine ratio (UACR) with SGLT-2 inhibition. In addition to these surrogate outcomes, SGLT-2 inhibitors also had a positive effect on clinical renal composite outcomes. For instance, in the secondary analysis of EMPA-REG, empagliflozin decreased the composite renal outcome (doubling of serum creatinine, renal replacement therapy or renal death) by 46%. Similar effects were also observed in the meta-analysis of CANVAS, DECLARE and CV outcomes studies.[29]

Empagliflozin decelerated renal disease progression (mild reduction in albuminuria and GFR) and provided mild improvements in end-stage renal disease (ESRD) development in T2DM patients with established ASCVD in EMPAREG OUTCOME.[1,50] The short- and long-term effect of empagliflozin on UACR appears to be independent of baseline albuminuria.[52] The decreases in major CV events, hospitalization for HF and mortality are consistent across all GFR and UACR categories.[53]

Annual reduction of eGFR was decreased by 40%, albuminuria progression declined by 27% and there was a numerical decrease in ESRD progression, although not statistically significant, with canagliflozin compared to placebo in the CANVAS program.[2,54] The effect on renal outcomes appear to be similar in all GFR subgroups of the primary and secondary CV prevention cohorts.[41,55]

In DECLARE TIMI-58, a 24% decrease was observed in the composite renal outcomes (>40% decline in GFR to <60 mL/min/1.73 m^2, ESRD or renal/CV death) with dapagliflozin.[3,56] The effect of dapagliflozin on albuminuria and analysis of renal outcomes according to baseline GFR were not reported in this study. In a subanalysis of DECLARE based on whether patients had previous MI,[56] renal outcomes were found to be worse in those with history of MI (8.4%–4.8%, 1.53; 1.25–1.89, p<0.001). However, the meta-analysis of CV outcome studies with SGLT-2 inhibitors did not support this finding.[29] According to the result of the meta-analysis, SGLT-2 inhibition reduced renal disease progression by 45% (0.55; 0.48–0.64, p <0.0001) and its renal effects were independent of the presence of CV disease at baseline. With SGLT-2 inhibition, a significant and consistent benefit is achieved in renal outcomes (progression of kidney injury, ESRD or renal death) in patients with and without ASCVD (Table 6).

The effect of SGLT-2 inhibition on renal outcomes may vary depending on baseline renal function.[29] The highest level of preventive effect was seen in patients with preserved renal function. The risk reduction in the composite outcome (progression of kidney injury, ESRD or renal death) was 33% in patients with GFR <60, 44% in those with GFR 60-90 and 56% in patients with GFR ≥90 (interaction p-value = 0.0258) (Table 7). In contrast to renal outcomes, patients with impaired renal function at baseline were found to achieve a more pronounced reduction in hospitalization for HF with SGLT-2 inhibition.[29]

Because renal outcomes were analyzed as a secondary outcome in CV outcome studies and as the incidence of CKD was <30% among the study participants, the renal effects of SGLT-2 inhibition observed in CV outcome studies should be interpreted as a hypothesis-generating result. The study that actually investigates the renal effects of SGLT-2 inhibition on CKD is CREDENCE.[14]

In CREDENCE, which included patients with GFR 30–90 mL/min/1.73 m^2 and UACR >300–5000 mg/g, mean GFR was 56.2±18.2 mL/min/1.73 m^2, UACR was 927 mg/g and 59.8% of the patients had GFR <60 mL/min/1.73 m^2. The study was terminated prematurely due to the marked decrease in the primary composite renal outcome (doubling of serum creatinine which persisted for 30 days, ESRD or renal/CV death) with canagliflozin compared to placebo (HR=0.70, 95% CI 0.59–0.82, p=0.00001). The renal protective effect was achieved in all CKD groups across a broad spectrum independent of baseline GFR values. With nearly all of the patients (99.9%) receiving ACEI/ARB, the protective effect achieved with SGLT-2 inhibitors appears to be maintained and results from the ongoing

Table 5. Baseline renal function and renal outcomes in patients enrolled in long-term SGLT-2 inhibitors studies

Clinical study/outcome	Baseline GFR	Baseline UACR	Renal benefit
Empagliflozin EMPA-REG[1] New-onset or progressing nephropathy and new-onset albuminuria	74 ml/min/1.73 m^2	<30 mg/g, 59.4% >30–300 mg/g, 28.6% >300 mg/g, 11.0%	Nephropathy 39% ↓ Progression to macroalbuminuria ↓ Doubling of serum creatinine level ↓ Initiation of renal replacement therapy↓
Dapagliflozin DECLARE[3] Beneficial effect based on baseline GFR level and CV disease status	85.2 ml/min/1.73 m^2	13.1 mg/g	Decline in GFR by 40% or more to less than 60 mL/min/1.73 m^2 ↓ Composite risk of ESRD or renal death ↓ Prevention and decelerated progression of CKD in patients with T2DM, acute kidney injury risk 31% ↓
Canagliflozin CANVAS[2] New-onset albuminuria, new-onset renal failure	76.5 ml/min/1.73 m^2	12.3 mg/g	Acute kidney injury ↓ Albuminuria ↓ 40% decrease in GFR ↓ Renal replacement therapy ↓ Kidney injury-related death ↓
Canagliflozin CREDENCE[14] Composite risk of new-onset albuminuria, dialysis, transplantation or death due t renal disease in those with CKD	56.2 ml/min/1.73 m^2	927 mg/g	Acute kidney injury, albuminuria ↓ 40% decrease in GFR ↓ Renal replacement therapy ↓ Death from renal causes in acute kidney injury ↓ Doubling of serum creatinine ↓ Risk of dialysis and transplantation ↓ Risk of ESRD or renal death ↓

GFR: Estimated glomerular filtration rate; UACR: Urinary albumin/creatinine ratio; CKD: Chronic kidney disease.

DAPA-CKD and EMPA-KIDNEY studies are awaited with anticipation. DAPA-CKD included diabetic and non-diabetic CKD patients with GFR ≥25–<75 mL/min/1.73 m^2 and macroalbuminuria (ClinicalTrials.gov: NCT03036150) and EMPA-KIDNEY included normo-, micro- and macroalbuminuric CKD with GFR ≥20 to <45 mL/min/1.73 m^2 (ClinicalTrials.gov Identifier: NCT03594110). Currently, SGLT-2 inhibitors are not recommended due to the loss of glycemic effect in diabetics with GFR <45 mL/min/1.73 m^2; however, the results of the aforementioned studies are expected to show whether these agents may be used for renal protection purposes independent of the glycemic effect.

Effect of SGLT-2 inhibitors on renal clinical outcomes in patients with HFrEF

A robust evaluation on the renal effects of SGLT-2 inhibition in patients with HF cannot be performed since HF patients account for approximately 10% of the entire cohort in EMPAREG OUTCOME and DECLARE TIMI-58.[1,3] Thus, this analysis was not conducted in EMPAREG. The DECLARE study demonstrated comparable benefits in patients with HFrEF and those without HF, consistent with the reduced risk of renal outcomes in all cohorts [0.65 (0.28–1.50) and 0.52 (0.41–0.67), respectively]. The frequency of acute renal failure as an adverse event was reported at a similar rate between those with and without HF.[3]

In DAPA-HF, renal effects of SGLT-2 inhibition [worsening renal function (GFR reduced by 50%), ESRD (GFR <15 mL for 28 days, dialysis or renal transplantation), or renal death] in diabetic and non-diabetic HF patients were evaluated as a secondary endpoint.[4] In DAPA-HF, which excluded patients with GFR <30 mL/min/1.73 m^2, mean GFR was 66 mL/min/1.73 m^2 and the incidence of those with GFR

Table 6. Effect of SGLT-2 inhibition on the composite outcome of kidney injury progression, ESRD or renal death in those with atherosclerotic CV disease or multiple risk factors

	Patients		Rate ratio per 1000 patient-years		(%)	HR (95% Confidence interval)
	Treatment (n)	Placebo (n)	Treatment	Placebo		
Aterosklerotik kardiyovasküler hastalığı olanlar						
EMPA-REG[1]	4645	2323	6.3	11.5	31.0	0.54 (0.40–0.75)
CANVAS[54]	3756	2900	6.4	10.5	35.6	0.59 (0.44–0.79)
DECLARE[3]	3474	3500	4.7	8.6	33.4	0.55 (0.41–0.75)
Interaction p-value for atherosclerotic cardiovascular disease=0.71						
Patients with multiple risk factors						
CANVAS[54]	2039	1447	4.1	6.6	29.5	0.63 (0.39–1.02)
DECLARE[3]	5108	5078	3.0	5.9	70.5	0.51 (0.37–0.69)
Interaction p-value for those with multiple risk factors=0.71						

HR: Risk ratio; HF: Heart failure; ESRD: End-stage renal disease; SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors.

Table 7. Effect of SGLT-2 inhibition on the composite outcome of kidney injury progression, ESRD or renal death based on baseline GFR level

	Patients		Rate ratio per 1000 patient-years		(%)	HR (95% Confidence interval)
	Treatment (n)	Placebo (n)	Treatment	Placebo		
GFH <60 mL/min/m^2						
EMPA-REG[1]	1196	605	NA	NA	33.5	0.66 (0.41–1.07)
CANVAS[54]	VY	VY	11.4	15.1	39.6	0.74 (0.48–1.15)
DECLARE[3]	606	659	8.9	15.2	27.0	0.60 (0.35–1.02)
GFH 60 - <90 mL/min/m^2						
EMPA-REG[1]	2406	1232	NA	NA	16.8	0.61 (0.37–1.03)
CANVAS[54]	VY	VY	4.6	7.4	34.4	0.58 (0.41–0.84)
DECLARE[3]	3838	3894	4.2	7.8	48.9	0.54 (0.40–0.73)
GFH ≥ 90 mL/min/m^2						
EMPA-REG[1]	1043	486	VY	VY	11.7	0.21 (0.09–0.53)
CANVAS[54]	VY	VY	3.8	8.1	27.5	0.44 (0.25–0.78)
DECLARE[3]	4137	4025	2.5	4.9	60.8	0.50 (0.34–0.73)
GFH için etkileşim p değeri=0.0258						

GFR: Estimated glomerular filtration rate; HR: Hazard ratio; ND: No data available; ESRD: End-stage renal disease; SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors.

<60 was approximately 40%. With a mean follow-up of 18.2 months, SGLT-2 inhibition was not different in terms of renal outcomes in patients with HF compared to placebo [rate ratio 0.8 for dapagliflozin and 1.2 for placebo per 1,000 patient-years, 0.71 (0.44–1.16)]. Acute kidney injury, classified as a serious adverse effect, developed less commonly in the dapagliflozin group (1.0% vs. 1.9%, p=0.007). Results

from the ongoing studies are expected to clarify the renal effects of SGLT-2 inhibitors in HFrEF.

A total of 101 cases of acute kidney injury, potentially drug-related, have been reported since SGLT-2 inhibitors have been introduced to use (reports up to 17 May 2016, www.accessdata.fda.gov/drugsatfda_docs/ Iabel/2016/204042s015s0191bl.pdf). About half of these occurred in the first month of treatment, and most of these events resolved after discontinuation of the drug. History of CKD, fluid loss, hypotension, or use of other drugs affecting the kidneys remain unknown in these patients. In an analysis performed after the case reports, there was no increased risk of acute kidney injury in those using SGLT-2 inhibitors.[58] Currently, it is recommended that renal function tests are performed prior to the use of SGLT-2 inhibitors and during follow-up, and drugs that may predispose the individual to acute renal disease (nonsteroidal anti-inflammatory agents) are not used concomitantly.

SGLT-2 Inhibitors in the Management of Diuretic Resistance and Combination of Diuretics

Şerafettin Demir

Current knowledge concerning the use of SGLT-2 inhibitors in combination with diuretics in the treatment of heart failure appear to be limited. This necessitates a study on the acute and long-term effects of using SGLT-2 inhibitors in combination with loop diuretics on renal function in patients with HF. A post hoc analysis of EMPA-REG conducted by Fitchett et al.[37] reported that the use of furosemide decreased in patients in the empagliflozin arm and that these patients had reached a relative state of euvolemia.[59] In T2DM patients, a marked increase in urinary sodium excretion was observed in the early stage of treatment with canagliflozin and empagliflozin.[60–62] In particular, dapagliflozin was shown to reduce plasma volume similar to the extent achieved with thiazide diuretics, although with a more persistent diuretic effect than diuretics. Interestingly, treatment of T2DM patients with dapagliflozin also provides a significant reduction in sodium concentrations in patients' skin.[63]

Currently, there is no comprehensive clinical study evaluating the effect of SGLT-2 inhibitors on diuresis in HF patients with diuretic resistance. However, a Japanese case report for the first time reported successful improvement of excessive fluid load with ipragliflozin 50 mg treatment for five days in a non-diabetic patient with diuretic resistance.[64] Moreover, Nordi et al.[65] currently investigate the effects of empagliflozin combined with loop diuretics on diuresis and diuretic resistance in RECEDE-CHF. In a recent study by Wilcox et al.,[66] which investigated adding dapagliflozin to treatment in healthy subjects receiving bumetanide and adding bumetanide to treatment in healthy subjects receiving dapagliflozin, natriuretic response was increased in both study arms and a synergistic effect was observed between bumetanide and dapagliflozin.

A recent position paper from the Heart Failure Association of the ESC concerning the use of diuretics has recommended that SGLT-2 inhibitors may be used for the treatment of diuretic resistance.[67] In this context, combination of loop diuretics and maximum dose increase are recommended in patients with diuretic resistance, and thiazide diuretics are recommended in first-line in the absence of an adequate diuresis response, followed by using acetazolamide or amiloride in second-line and addition of SGLT-2 inhibitors to treatment in third-line setting.[67] Therefore, it should be taken into account that SGLT-2 inhibitors may potentiate the effect of diuretics in patients with HF and provide an alternative treatment approach to overcome diuretic resistance.

Undesirable Effects of SGLT-2 Inhibitors and Management

Ahmet Çelik

Side effects

Common and rare side effects of SGLT-2 inhibitors are summarized in Table 8.

Volume depletion

Due to the osmotic/diuretic effects of SGLT-2 inhibitors, side effects associated with volume depletion have been observed in several cases. Side effects associated with volume depletion in the EMPA-REG study were similar across the empagliflozin 10 mg and 25 mg arms and the patients receiving placebo.[1] In CANVAS, rate ratio per 1000 patient-years was 26 in patients on canagliflozin and 18.5 in the patient group receiving placebo (p=0.009).[2] In DECLARE, symptoms of volume depletion occurred in 2.5% of

Table 8. Side effects of SGLT-2 inhibitors

Common side effects	Rare side effects
Volume depletion	Diabetic ketoacidosis
Genital tract infections	Distal lower extremity amputations
Urinary tract infections	Bone fractures
	Acute renal failure
	Fournier's gangrene
	Bladder cancer
	Hypoglycemia

the dapagliflozin group, while this rate was similar at 2.4% in the placebo group (p=0.99).[3]

Volume depletion may occur more commonly in patients receiving ACEI/ARB and/or diuretics. In these patients, it should be taken into account that addition of SGLT-2 inhibitors to treatment may cause dehydration, dizziness, blackout, hypotension and syncope and each patient's volume status should be assessed carefully before starting treatment, with dose reduction to be implemented upon the initiation of SGLT-2 inhibitors especially in patients on diuretics.

Hypoglycemia

Although SGLT-2 inhibition is achieved with this group of drugs, hypoglycemia is not expected with SGLT-2 inhibitors since renal glucose reabsorption continues through SGLT-1 receptors.[68] In fact, phase 3 studies with empagliflozin, canagliflozin and dapagliflozin revealed a similar incidence of major hypoglycemic events in the patient groups receiving medication compared to those receiving placebo.[1–3] However, although low, a risk of hypoglycemia cannot be ruled out with the concomitant use of insulin or insulin secretagogues. When SGLT-2 inhibitors are considered for patients on insulin or insulin secretagogues, it may be feasible to reduce the insulin dose in order to avoid hypoglycemic episodes.

Diabetic ketoacidosis

Phase III studies have shown a low rate of this complication in patients receiving treatment with SGLT-2 inhibitors. The incidence was very low and similar to placebo group with empagliflozin while it was slightly higher with canagliflozin, and the recently published DECLARE-TIMI-58 reported a higher incidence in patients receiving dapagliflozin compared to placebo group.[1–3] Real-world data from Europe have shown a significantly higher incidence of diabetic ketoacidosis in patients receiving treatment with SGLT-2 inhibitors (mostly empagliflozin and dapagliflozin) compared to those receiving GLP-1 agonists.[69]

Euglycemic diabetic ketoacidosis was observed in patients on SGLT-2 inhibitors and both European Medicines Agency and FDA have been notified of this finding. American Association of Clinical Endocrinologists recommends discontinuation of SGLT-2 inhibitors 24 hours before elective surgery or planned invasive procedures; avoidance of rigorous physical activity, abrupt discontinuation or severe dose reduction of insulin, consumption of excessive alcohol and/or very low carbohydrate or ketogenic diets in order to minimize the risk of diabetic ketoacidosis associated with SGLT-2 inhibitors.[70]

Acute renal failure

SGLT-2 inhibitors may potentially cause acute kidney injury through a number of pathways including volume depletion especially in patients with dehydration or those receiving heavy diuretic treatment, reduction of transglomerular pressure (particularly in patients receiving renin-angiotensin-aldosterone blockers) and renal medullary hypoxic damage.[71] On the other hand, rates of the composite renal outcomes in the 3 large randomized controlled trials, i.e. progression to macroalbuminuria, doubling of serum creatinine, ESRD or death due to renal causes have shown that SGLT-2 inhibitors decreased renal outcomes compared to placebo in EMPA-REG, CANVAS and DECLARE.[3,50,54]

Furthermore, real-world data comparing 6,418 patients starting treatment with SGLT-2 inhibitors versus 5,604 patients starting treatment with DPP-4 inhibitors revealed a lower incidence of acute kidney injury in those receiving SGLT-2 inhibitors compared to those receiving DPP-4.[72] In a propensity score matching study using data from Denmark and Sweden, 17,213 patients receiving SGLT-2 inhibitors were compared with 17,213 patients receiving GLP-1 agonists and the two drug groups were found to be similar in terms of acute kidney injury, with a more favorable trend of kidney injury in the SGLT-2 inhibitors group.[69]

Genital tract infections

Genital tract infections (mostly vaginitis in women and balanitis in men) were more common in all pati-

ents using SGLT-2 inhibitors than placebo. Especially female patients with previous history of genital tract infections and male patients without circumcision were demonstrated to be at higher risk.[68] Although more common in female patients than in males, these infections generally develop with mild or moderate severity and patients often respond well to classical antifungal therapies. Rates of discontinuation due to genital tract infections associated with SGLT-2 inhibitors use were relatively low in all randomized controlled trials.[1–3]

Fournier's Gangrene

Fournier's gangrene, also known as necrotizing infection of the perineum and perianal region, is an extremely important condition with high morbidity and mortality that may require multiple surgical interventions. Patients with DM are known to be at a higher risk of Fournier's gangrene. In 2018, the FDA issued a warning about SGLT-2 inhibitors and stated that 55 patients receiving SGLT-2 inhibitors, which have been in use for the past 6 years, had Fournier gangrene while 19 cases have been observed with other oral anti-diabetic drugs through 35 years, emphasizing alertness among physician and vigilance for patients treated with SGLT-2 inhibitors in this regard.[73] Only a limited number of these cases have been reported in the literature.[74–76]

However, results from EMPAREG OUTCOME and CANVAS did not reveal whether Fournier's gangrene developed in any of the patients included in these studies.[1,2] The DECLARE study, on the other hand, reported Fournier's gangrene in 6 patients, with 5 in the placebo arm and 1 in the dapagliflozin arm across a larger patient population compared to other studies.[3] Fournier's gangrene appears to be a considerably rare side effect, especially in large randomized studies, with a greater number of patients experiencing this event in the placebo arm compared to the dapagliflozin arm of DECLARE, and it is therefore not applicable to conclude that SGLT-2 inhibitors increase the development of Fournier's gangrene at this point.

Urinary tract infections

T2DM patients are at a 60% higher risk of bacterial urinary tract infections than individuals without diabetes. In addition, asymptomatic bacteriuria is more common in T2DM patients than those without diabetes.[77] Although urinary tract infections are reported in patients receiving SGLT-2 inhibitors, major studies such as EMPAREG, CANVAS and DECLARE have reported that urinary tract infections were similar in the placebo group and the drug group in all patients receiving the three SGLT-2 inhibitors.[1–3] Meta-analyses performed at different time points reported that SGLT-2 inhibitors did not increase the risk of urinary tract infections.[78–84]

Cancer

In EMPAREG, DECLARE and CANVAS, the rate of cancer development was similar in patients receiving empagliflozin, dapagliflozin and canagliflozin compared to those on placebo.[1–3] In the DECLARE study, bladder cancer was less common in patients receiving dapagliflozin than placebo (0.3 vs 0.5%; HR=0.57, 95% CI=0.35–0.93; p=0.02). The meta-analysis of 49 independent randomized controlled trials including a total of 34,569 patients determined 580 cancer cases where SGLT-2 inhibitors did not appear to increase the cancer risk overall [OR 1.14 [95% CI=0.96, 1.36)]; however, the risk of bladder cancer was considered to be potentially associated with SGLT-2 inhibitors [OR 3.87 (95% CI=1.48, 10.08)], in particular with empagliflozin [OR 4.49 (95% CI=1.21, 16.73)], and canagliflozin was found to cause significantly less gastrointestinal cancers compared to placebo.[85]

Bone fractures

SGLT-2 inhibitors are thought to alter calcium and phosphate hemostasis due to the phosphate reabsorption caused by secondary hyperparathyroidism, thereby potentially affecting bone mass and lead to a risk of fractures.[86] Taking into account the large randomized controlled studies, the incidence of bone fractures with empagliflozin and dapagliflozin appear to be no different than placebo. However, when all fractures in patients receiving canagliflozin were evaluated, the incidence of fractures per 1000 patient-years was found to 15.4% in the canagliflozin arm and 11.9% in the placebo arm (p=0.02). FDA issued a warning on canagliflozin in 2015.[87] The recently published meta-analyses did not reveal any increase in the risk of bone fractures in patients treated with SGLT-2 inhibitors.[88–90]

Lower extremity amputations

The CANVAS study reported that lower extremity amputations were significantly higher in the canagliflozin group compared to placebo.[2]

It was found that amputations were localized especially at the toe or metatarsal level, and the risk was similar in patients with and without peripheral artery disease as well as those with and without previous amputation.[2] However, the same side effects were not seen with empagliflozin and dapagliflozin.[1,3] In a retrospective cohort study of 953,960 patients, 39,120 patients receiving SGLT-2 inhibitors were compared with patients on other oral antidiabetic by means of the propensity score matching method and amputation rates in the lower extremity were also reported. Compared to patients using DPP-4 inhibitors and GLP-1 agonists, those treated with SGLT-2 inhibitors had numerically higher rates of amputation in the lower extremities; however, the difference was not statistically significant. On the other hand, the rates of amputation in lower extremities was significantly higher in patients receiving SGLT-2 inhibitors (corrected hazard ratio, 2.12; 95% CI=1.19-3.77) compared to those using sulfonylurea, metformin or thiazolidinedione.[91]

In a meta-analysis of 14 recently published randomized controlled trials, 26,167 patients were investigated in terms of diabetic foot and amputation risk and no relationship was found between SGLT-2 inhibitors and the risk of diabetic foot development (OR=1.05, 95% CI=0.58–1.89). Although SGLT-2 inhibitors were found to cause no statistically significant increase in amputation risk across all patients receiving these agents (OR=1.40, 95% CI=0.81–2.41), it was reported that the incidence of amputation was significantly higher in patients treated with canagliflozin in the subgroup analysis (OR=1.89, 95% CI=1.37–2.60).[92] In a propensity score matching study using data from Norway and Sweden, 17,213 patients receiving SGLT-2 inhibitors were compared with 17,213 patients receiving GLP-1 agonists and although the rate of those using canagliflozin was only 1%, the risk of amputation was found to be two-fold higher in those treated with SGLT-2 inhibitors compared to patients treated with GLP-1 agonists. This finding led to the suspicion that this side effect may in fact be a rare class effect.[69]

The side effect rates in the 3 large randomized studies completed to date are summarized in Table 9.

Contraindications

In the current clinical practice, empagliflozin, dapagliflozin and canagliflozin are not recommended for use in DM patients with GFR values below 45 mL/min/1.73 m^2. This threshold is 60 mL/min/1.73 m^2 for ertugliflozin. However, the CV outcome studies (EMPA-REG, CANVAS, DAPA-HF) included patients with GFR down to 30 mL/min/1.73 m^2 and revealed improvement in renal clinical outcomes. Therefore, one may conclude that empagliflozin, dapagliflozin and canagliflozin may be used in patients with GFR down to 30 mL/min/1.73 m^2. The ongoing

Table 9. Comparative illustration of side effects seen in the EMPA-REG OUTCOME, DECLARE-TIMI58 and CANVAS studies with SGLT-2 inhibitors

	EMPA-REG		DECLARE		CANVAS*	
Rate of side effect occurrence, %	EMPA	PLACEBO	DAPA	PLACEBO	KANA	PLACEBO
Complicated urinary infection	1.7	1.8	1.5	1.6	40	37
Genital infection	6.4	1.8	0.9	0.1	34.9 E 68.8 K	10.8 E 17.5 K
Diabetic ketoacidosis	0.1	<0.1	0.3	0.1	0.6	0.3
Bone fractures	3.8	3.9	5.3	5.1	15.4	11.9
Lower extremity amputations	BY	BY	1.4	1.3	6.3	3.4
Severe hypoglycemia	1.3	1.5	0.7	1.0	50	46.4
Volume depletion	5.1	4.9	2.5	2.4	26	18.5
Cancer	BY	BY	5.6	5.7	4.7	3.9
Acute renal failure	5.2	6.6	1.5	2.0	3.0	4.1
Severe side effects requiring drug discontinuation	17.3	19.4	8.1	6.9	35.5	32.8

*Rate ratio per thousand patient-years. EMPA: Empagliflozin; DAPA: Dapagliflozin; CANA: Canagliflozin; NI: No information available; M: Male; F: Female.

studies are expected to provide insight on whether a lower threshold may be utilized in this context. SGLT-2 inhibitors are contraindicated in patients with known history of serious hypersensitivity reactions to these agents.[93,96]

Consensus Treatment Algorithm Including SGLT-2 Inhibitors in Heart Failure with Low Ejection Fraction

The treatment algorithm including SGLT-2 inhibitors

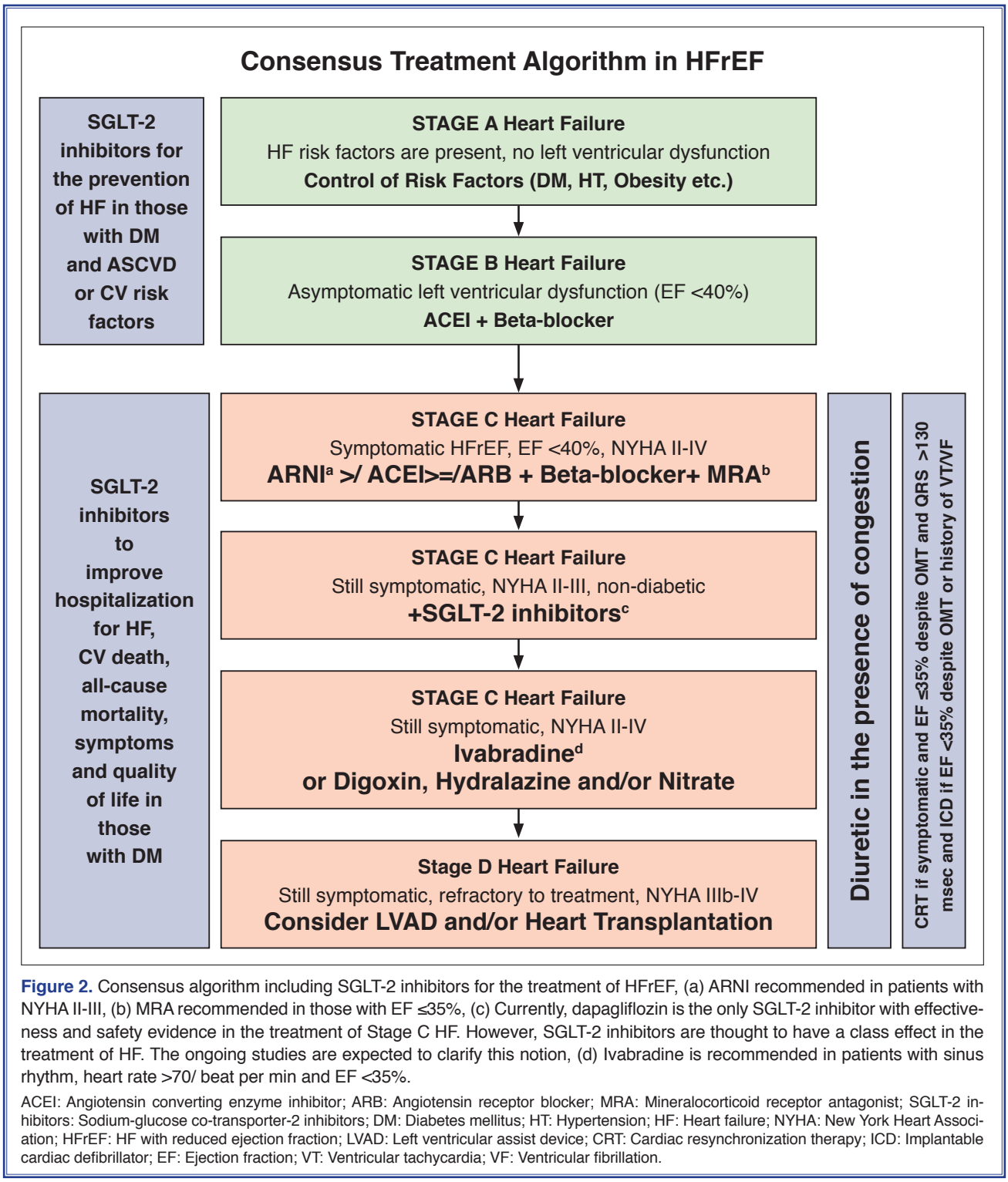

Figure 2. Consensus algorithm including SGLT-2 inhibitors for the treatment of HFrEF, (a) ARNI recommended in patients with NYHA II-III, (b) MRA recommended in those with EF ≤35%, (c) Currently, dapagliflozin is the only SGLT-2 inhibitor with effectiveness and safety evidence in the treatment of Stage C HF. However, SGLT-2 inhibitors are thought to have a class effect in the treatment of HF. The ongoing studies are expected to clarify this notion, (d) Ivabradine is recommended in patients with sinus rhythm, heart rate >70/ beat per min and EF <35%.

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonist; SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors; DM: Diabetes mellitus; HT: Hypertension; HF: Heart failure; NYHA: New York Heart Association; HFrEF: HF with reduced ejection fraction; LVAD: Left ventricular assist device; CRT: Cardiac resynchronization therapy; ICD: Implantable cardiac defibrillator; EF: Ejection fraction; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

in HFrEF based on currently available evidence is presented in Figure 2.

What does the future hold for SGLT2 inhibitors?

Itamar Raz, Avivid Cahan

SGLT-2 inhibitors in patients with T2DM at high CV risk

SGLT-2 inhibitors have been approved for the treatment of T2DM since 2012. These agents lead to a reduction in glucose as well as weight and blood pressure, thus addressing multiple aspects of the metabolic syndrome.[97]

The EMPA-REG study, the first completed cardiovascular outcome study of an SGTL-2 inhibitors-empagliflozin demonstrated robust reduction in major adverse cardiovascular events (MACE), hospitalization for HF, as well as marked improvement in renal outcomes.[1,50] CV death was significantly reduced with empagliflozin, thus, the U.S. Food and Drug Administration (FDA) approved a new indication for empagliflozin - to reduce the risk of CV death in adult patients with T2DM and CV disease. All patients included in the study had established ASCVD, thus the effect of these agents on the primary prevention of CV events in patients with diabetes remained unknown.

CANVAS program, which was subsequently published, included a high-risk patient population with T2DM with and without ASCVD, although the majority had established ASCVD. A reduction in MACE was observed with canagliflozin vs. placebo, as well as reduction in hospitalization for HF and adverse renal outcomes.[2]

CREDENCE study assessed renal outcomes of canagliflozin vs. placebo in patients with T2DM and diabetic kidney disease (eGFR <90 and 300–5000 mg/gr albuminuria). The trial was terminated early, after 2.6 years, having attained superiority in its primary endpoint (end stage renal disease, doubling of serum creatinine or death from renal or CV causes).[14] Based on this study, the FDA approved a new indication for canagliflozin - to reduce the risk of end-stage renal disease (ESRD), worsening of kidney function, CV death, and hospitalization for HF in adults with T2DM and diabetic kidney disease.

DECLARE -TIMI 58 study included a large primary prevention population, as well as a secondary prevention population. An overall reduction in the composite of CV death and hospitalization for HF with dapagliflozin vs. placebo was observed as well as robust reduction in the rate of decline in renal function.[3] MACEs were balanced between groups, but were reduced with dapagliflozin vs. placebo in those with prior myocardial infarction.[57] These effects were of similar magnitude at all age groups included in the study (40 and above, per inclusion criteria).[3] Moreover, dapagliflozin was overall safe, at all age groups studied (including >65 and >75 years) and no increased risk for hypovolemia, fractures, cancer or urinary tract infections was noted.[98] Acute kidney injury and major hyperglycemia were also reduced irrespective of age, and ketoacidosis as well as genital infections were increased, in line with what had been shown for other agents in the class.[29]

Based on the HF hospitalization reduction observed in the DECLARE-TIMI 58 study, in which it was defined as part of the composite co-primary outcome - the FDA approved dapagliflozin to reduce the risk of hospitalization for HF for patients with T2DM and established ASCVD or multiple cardiovascular risk factors.

Overall, SGLT-2 inhibitors have emerged as medications to treat patients with T2DM with benefits far exceeding glucose lowering alone. Besides their effects on lowering weight and blood pressure, specific agents in the class are already indicated for the reduction of CV death, HF hospitalization and for the treatment of diabetic kidney disease in patients with diabetes. Still, these trials have focused on patients with T2DM at high risk for, or established ASCVD, and their effects on low CV risk T2DM patients are not yet established. Moreover, the role of SGLT-2 inhibitors in the care of patients with T2DM is expanding, as is their role in the treatment of additional medical conditions.

SGLT-2 inhibitors in patients with type 2 diabetes and low cardiovascular risk

The recently described studies have been conducted in patients with established ASCVD, and the DECLARE-TIMI 58 also included a broad population with risk factors for, but not established ASCVD. The HF and renal benefits observed in these trials were consistent, irrespective of risk status – supporting the use of these drugs for primary prevention of renal deterioration and HF in high risk populations.[29] Moreover, the renal benefits observed with dapagliflozin were irrespective of baseline eGFR or albuminuria – sup-

porting its use in primary prevention of adverse renal outcomes as well.[56] Still, low risk individuals were not included in any of these studies.

Recent guidelines proposed positioning drugs with an established cardio-protective benefit as first line for patients with established ASCVD or at high risk, while leaving metformin's hegemony as first line therapy for low risk patients.[31] However, due to the multiple metabolic benefits offered by SGLT-2 inhibitors, initial combination therapy with both metformin and SGLT-2 inhibitors may be considered in low risk patients as well. Initial combination therapy with metformin and a DPP4 inhibitor demonstrated greater glycemic durability compared to metformin alone further supporting the initial combination approach.[99] Nevertheless, due to possible medication side effects, contra-indications (mainly low eGFR) and financial barriers, it is may be more prudent to prescribe this medication primarily to those at high baseline risk for HF or CKD. We have recently proposed a risk score for HF hospitalization based on the placebo group of the SAVOR trial (8,200 patients) and this score can be used in combination with bio-markers such as pro-BNP and troponin to identify high risk patients.[100]

SGLT-2 inhibitors in patients with type 1 diabetes

Several studies have shown significant glycemic and weight benefit in patients with type 1 diabetes, and dapagliflozin and sotagliflozin have been approved for use in these patients in Europe.[101]

Although an increase in rates of DKA is observed with all agents, and the absolute risk is much greater in patients with T1DM, these drugs are actually the first breakthrough in years in the medical treatment of patients with T1DM.

SGLT-2 inhibitors in patients with pre-diabetes or euglycemia

The role of SGLT-2 inhibitors in the prevention of diabetes in high risk patients has not been studied, and it is unlikely that such clinical studies will be conducted. SGLT-2 inhibitors appear to have no direct role on beta cell protection, and the beta-cell protective effects noted are mediated probably by glycemia alone.[102] Nevertheless, the role of these agents in patients who are at high risk for HF suffering of pre-diabetes, obesity, or post MI patients with no apparent HF remains to be assessed. DAPA-HF trial included patients with HFrEF, both with and without diabetes. The study demonstrated a reduction in the risk of worsening HF regardless of the patients' glycemic status.[4] Studies on patients with HFpEF are ongoing.

HF is a prevalent comorbidity in patients with diabetes, pre-diabetes and the metabolic syndrome. The inclusion of SGLT-2 inhibitors in the treatment regimen of pre-diabetic patients may reduce the risk for HF. Moreover, utilizing a HF risk score and future development of echocardiographic and serum biomarkers may further delineate those who may benefit the most from these agents.

SGLT-2 inhibitors have shown a robust renal-protective effect in patients with diabetes, and reduce blood pressure, albuminuria and slow the rate of eGFR decline. Their role in the treatment, or even prevention, of hypertensive kidney disease, or other forms of chronic kidney disease in euglycemic patients is currently being assessed.

Conclusions

SGLT-2 inhibitors which had initially been developed solely as glucose lowering agents revolutionized not only diabetes care, but are also emerging as key drugs in the treatment and prevention of both heart failure and chronic kidney disease. Future research and development will surely expand the indications of this pleiotropic drug class.

Peer reviewer: External independent.

Conflict of Interest: None.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015;373:2117–28.
2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644–57.
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019;380:347–57.
4. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995–2008.

5. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, et al. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation 2019;140:1463–76.
6. Karg MV, Bosch A, Kannenkeril D, Striepe K, Ott C, Schneider MP, et al. SGLT-2-inhibition with dapagliflozin reduces tissue sodium content: a randomised controlled trial. Cardiovasc Diabetol 2018;17:5.
7. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, et al. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2018;41:356–63.
8. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab 2018;20:479–87.
9. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, Chen L. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018;20:458–62.
10. Schork A, Saynisch J, Vosseler A, Jaghutriz BA, Heyne N, Peter A, et al. Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy. Cardiovasc Diabetol 2019;18:46.
11. Zhao D, Liu H, Dong P. Empagliflozin reduces blood pressure and uric acid in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. J Hum Hypertens 2019;33:327–39.
12. Ferdinand KC, Izzo JL, Lee J, Meng L, George J, Salsali A, et al. Antihyperglycemic and Blood Pressure Effects of Empagliflozin in Black Patients With Type 2 Diabetes Mellitus and Hypertension. Circulation 2019;139:2098–109.
13. Kashiwagi A, Maegawa H. Metabolic and hemodynamic effects of sodium-dependent glucose cotransporter 2 inhibitors on cardio-renal protection in the treatment of patients with type 2 diabetes mellitus. J Diabetes Investig 2017;8:416–27.
14. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019;380:2295–306.
15. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, et al. Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia 2017;60:568–73.
16. Lee TI, Chen YC, Lin YK, Chung CC, Lu YY, Kao YH, et al. Empagliflozin Attenuates Myocardial Sodium and Calcium Dysregulation and Reverses Cardiac Remodeling in Streptozotocin-Induced Diabetic Rats. Int J Mol Sci 2019;20:1680.
17. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res 2015;12:78–89.
18. Durak A, Olgar Y, Degirmenci S, Akkus E, Tuncay E, Turan B. A SGLT2 inhibitor dapagliflozin suppresses prolonged ventricular-repolarization through augmentation of mitochondrial function in insulin-resistant metabolic syndrome rats. Cardiovasc Diabetol 2018;17:144.
19. Li C, Zhang J, Xue M, Li X, Han F, Liu X, et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. Cardiovasc Diabetol 2019;18:15.
20. Papademetriou V, Geladari E. Sodium-glucose Cotransporter 2 Inhibitors: The Impact on Development and Progression of Heart Failure. Cardiovasc Hematol Disord Drug Targets 2018;18:127–133.
21. Kalra S, Jain A, Ved J, Unnikrishnan AG. Sodium-glucose cotransporter 2 inhibition and health benefits: The Robin Hood effect. Indian J Endocrinol Metab 2016;20:725–9.
22. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care 2016;39:1108–14.
23. Yurista SR, Silljé HHW, Oberdorf-Maass SU, Schouten EM, Pavez Giani MG, Hillebrands JL, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail 2019;21:862–73.
24. Oh CM, Cho S, Jang JY, Kim H, Chun S, Choi M, et al. Cardioprotective Potential of an SGLT2 Inhibitor Against Doxorubicin-Induced Heart Failure. Korean Circ J 2019;49:1183–95.
25. Yoshioka H, Ohishi R, Hirose Y, Torii-Goto A, Park SJ, Miura N, et al. Chronopharmacology of dapagliflozin-induced antihyperglycemic effects in C57BL/6J mice. Obes Res Clin Pract 2019;13:505–10.
26. Díaz-Rodríguez E, Agra RM, Fernández ÁL, Adrio B, García-Caballero T, González-Juanatey JR, et al. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. Cardiovasc Res 2018;114:336–46.
27. Gaspari T, Spizzo I, Liu H, Hu Y, Simpson RW, Widdop RE, et al. Dapagliflozin attenuates human vascular endothelial cell activation and induces vasorelaxation: A potential mechanism for inhibition of atherogenesis. Diab Vasc Dis Res 2018;15:64–73.
28. Cintra RMR, Soares AAS, Breder I, Munhoz DB, Barreto J, Kimura-Medorima ST, et al. ADDENDA-BHS2 trial investigators. Assessment of dapagliflozin effect on diabetic endothelial dysfunction of brachial artery (ADDENDA-BHS2 trial): rationale, design, and baseline characteristics of a randomized controlled trial. Diabetol Metab Syndr 2019;11:62.
29. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–9.

30. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37: 2129–200.
31. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Eur Heart J 2020;41: 255–323.
32. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:1169–86.
33. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J 2008;29:1224–40.
34. Wallner M, Eaton DM, von Lewinski D, Sourij H. Revisiting the Diabetes-Heart Failure Connection. Curr Diab Rep 2018;18:134.
35. Fitchett D, Butler J, van de Borne P, Zinman B, Lachin JM, Wanner C, et al. EMPA-REG OUTCOME® trial investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J 2018;39:363–70.
36. Figtree GA, Rådholm K, Barrett TD, Perkovic V, Mahaffey KW, de Zeeuw D, et al. Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus. Circulation 2019;139:2591–3.
37. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. EMPA-REG OUTCOME® trial investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 2016;37:1526–34.
38. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus. Circulation. 2018;138:458–68.
39. 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;139:2528–36.
40. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail 2019;21:1402–11.
41. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, et al. CANVAS Program Collaborative Group. Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;137:323–34.
42. Lan NSR, Fegan PG, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. ESC Heart Fail 2019;6:927–35.
43. Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:1845–55.
44. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382:260–72.
45. Gembardt F, Bartaun C, Jarzebska N, Mayoux E, Todorov VT, Hohenstein B, et al. The SGLT2 inhibitor empagliflozin ameliorates early features of diabetic nephropathy in BTBR ob/ob type 2 diabetic mice with and without hypertension. Am J Physiol Renal Physiol 2014;307:F317–25.
46. Terami N, Ogawa D, Tachibana H, Hatanaka T, Wada J, Nakatsuka A, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLoS One 2014;9:e100777.
47. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013;15:463–73.
48. Yamout H, Perkovic V, Davies M, Woo V, de Zeeuw D, Mayer C, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes and stage 3 nephropathy. Am J Nephrol 2014;40:64–74.
49. Dziuba J, Alperin P, Racketa J, Iloeje U, Goswami D, Hardy E, et al. Modeling effects of SGLT-2 inhibitor dapagliflozin treatment versus standard diabetes therapy on cardiovascular and microvascular outcomes. Diabetes Obes Metab 2014;16:628–35.
50. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016;375:323–34.
51. Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, et al. Class effects of SGLT2 inhibitors on cardiorenal outcomes. Cardiovasc Diabetol 2019;18:99.
52. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an

exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:610–21.

53. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 2018;137:119–29.
54. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691–704.
55. Neuen BL, Ohkuma T, Neal B, Matthews DR, de Zeeuw D, Mahaffey KW, et al. Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function. Circulation 2018;138:1537–50.
56. Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019;7:606–17.
57. 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;139:2516–27.
58. Nadkarni GN, Ferrandino R, Chang A, Surapaneni A, Chauhan K, Poojary P, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. Diabetes Care 2017;40:1479–85.
59. McMurray J. EMPA-REG - the "diuretic hypothesis". J Diabetes Complications 2016;30:3–4.
60. Tanaka H, Takano K, Iijima H, Kubo H, Maruyama N, Hashimoto T, et al. Factors Affecting Canagliflozin-Induced Transient Urine Volume Increase in Patients with Type 2 Diabetes Mellitus. Adv Ther 2017;34:436–51.
61. Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang SS, et al. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:1087–95.
62. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Barsotti E, Clerico A, et al. Renal Handling of Ketones in Response to Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 2 Diabetes. Diabetes Care 2017;40:771–6.
63. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab 2013;15:853–62.
64. Sairaku A, Nakano Y, Kihara Y. Increased urine output by ipragliflozin in a non-diabetic patient with a diuretic-resistant heart failure. Int J Cardiol 2015;180:42–3.
65. Mordi NA, Mordi IR, Singh JS, Baig F, Choy AM, McCrimmon RJ, et al. Renal and Cardiovascular Effects of sodium-glucose cotransporter 2 (SGLT2) inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure (RECEDE-CHF): protocol for a randomised controlled double-blind cross-over trial. BMJ Open 2017;7:e018097.
66. Wilcox CS, Shen W, Boulton DW, Leslie BR, Griffen SC. Interaction Between the Sodium-Glucose-Linked Transporter 2 Inhibitor Dapagliflozin and the Loop Diuretic Bumetanide in Normal Human Subjects. J Am Heart Assoc 2018;7:e007046.
67. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:137–55.
68. Filippas-Ntekouan S, Filippatos TD, Elisaf MS. SGLT2 inhibitors: are they safe?. Postgrad Med 2018;130:72–82.
69. Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ 2018;363:k4365.
70. Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, et al. American association of clinical endocrinologists and american college of endocrinology position statement on the association of sglt-2 inhibitors and diabetic ketoacidosis. Endocr Pract 2016;22:753–62.
71. Wanner C. EMPA-REG OUTCOME: The Nephrologist's Point of View. Am J Cardiol 2017;120:S59–67.
72. Cahn A, Melzer-Cohen C, Pollack R, Chodick G, Shalev V. Acute renal outcomes with sodium-glucose co-transporter-2 inhibitors: Real-world data analysis. Diabetes Obes Metab 2019;21:340–8.
73. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier Gangrene Associated With Sodium-Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. Ann Intern Med 2019;170:764–9.
74. Kumar S, Costello AJ, Colman PG. Fournier's gangrene in a man on empagliflozin for treatment of Type 2 diabetes. Diabet Med 2017;34:1646–8.
75. Omer TAM, Dharan SS, Adler A. Sodium–glucosecotransporter 2 (SGLT–2) inhibitor dapagliflozin and Fournier's gangrene: a life–threatening severe adverseoutcome. Case report. Diabet Med 2018;35:97–106.
76. Rodler S, Weig T, Finkenzeller C, Stief C, Staehler M. Fournier´s Gangrene Under Sodium-Glucose Cotransporter 2 Inhibitor Therapy as a Life-Threatening Adverse Event: A Case Report and Review of the Literature. Cureus 2019;11:e5778.
77. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Caminero A. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). J Diabetes Complications 2012;26:513–6
78. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:262–74.
79. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy

and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol 2014;70:1149–58.
80. Zhang M, Zhang L, Wu B, Song H, An Z, Li S. Dapagliflozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2014;30:204–21.
81. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984–93.
82. Liu XY, Zhang N, Chen R, Zhao JG, Yu P. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2years. J Diabetes Complications 2015;29:1295–303.
83. Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. Acta Diabetol 2018;55:503–14.
84. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. Diabetes Obes Metab 2017;19:348–55.
85. Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia 2017;60:1862–72.
86. Meier C, Schwartz AV, Egger A, Lecka-Czernik B. Effects of diabetes drugs on the skeleton. Bone 2016;82:93–100.
87. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDAreviseslabel of diabetes drugcanagliflozin (Invokana, Invokamet) toinclude updates on bone fracture risk and new information on decreased bone mineral density. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed Feb 28, 2020.
88. Tang HL, Li DD, Zhang JJ, Hsu YH, Wang TS, Zhai SD, et al. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. Diabetes Obes Metab 2016;18:1199–206.
89. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: A meta-analysis. Diabetes Metab Res Rev 2017;33:10.1002/dmrr.2903.
90. Azharuddin M, Adil M, Ghosh P, Sharma M. Sodium-glucose cotransporter 2 inhibitors and fracture risk in patients with type 2 diabetes mellitus: A systematic literature review and Bayesian network meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2018;146:180–90.
91. Chang HY, Singh S, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes. JAMA Intern Med 2018;178:1190–8.
92. Li D, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials. Diabetes Metab 2018;44:410–4.
93. Jardiance (empagliflozintablets, for oral use) [package Insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2018. Available at: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf. Accessed Feb 28, 2020.
94. Invokana (canagliflozintablets, for oral use) [package Insert]. Titusvlle, NJ: Janssen Pharmaceuticals, Inc.; 2018. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf. Accessed Feb 28, 2020.
95. Farixga (dapagliflozintablets, for oral use) [package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202293s015lbl.pdf. Accessed Feb 28, 2020.
96. Steglatro (ertugliflozintablets, for oral use) [package Insert]. Whitehouse Station, NJ: Merck Sharp&Dohme Corp; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf. Accessed Feb 28, 2020.
97. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015;75:33–59.
98. Cahn A, Mosenzon O, Wiviott SD, Rozenberg A, Yanuv I, Goodrich EL, et al. Efficacy and Safety of Dapagliflozin in the Elderly: Analysis From the DECLARE-TIMI 58 Study. Diabetes Car 2020;43:468–75.
99. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394:1519–29.
100. Berg DD, Wiviott SD, Scirica BM, Gurmu Y, Mosenzon O, Murphy SA, et al. Heart Failure Risk Stratification and Efficacy of Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes Mellitus. Circulation 2019;140:1569–77.
101. Taylor SI, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. Lancet Diabetes Endocrinol 2019;7:949–58.
102. Merovci A, Mari A, Solis-Herrera C, Xiong J, Daniele G, Chavez-Velazquez A, et al. Dapagliflozin lowers plasma glucose concentration and improves β-cell function. J Clin Endocrinol Metab 2015;100:1927–32.

Keywords: Diabetes mellitus; heart failure; SGLT-2 inhibitors.

Anahtar sözcükler: Diyabet; kalp yetersizliği; SGLT-2 inhibitörleri.