REVIEW ARTICLE

Sodium-glucose cotransporter-2 inhibitors in obesity and associated cardiometabolic disorders: where do we stand?

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KEY WORDS

cardiometabolic disorders, cardiovascular disease, diabetes, obesity, SGLT-2 inhibitors

ABSTRACT

As the tide of obesity and its complications are on the rise, there is an urgent need for new drugs with weight-lowering and beneficial metabolic properties. Obesity-related disorders, such as metabolic syndrome, prediabetes, type 2 diabetes (T2D), cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD) make this need more than mandatory. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) are the latest class of agents to receive approval for the treatment of T2D. Not long after their marketing, a wide spectrum of target organ-protective and overall beneficial health effects associated with their use began to unveil. An increasing bulk of evidence indicates that these actions are to a great degree independent of glucose lowering, which has led to the broadening of the indications for SGLT-2 inhibitors outside the frame of antihyperglycemic therapy. Additionally, their unique mode of action including increased renal glucose excretion, and hence net energy loss, could render SGLT-2 inhibitors attractive candidates for the treatment of obesity. Very few reviews in the literature have holistically appraised the therapeutic potential of SGLT-2 inhibitors in obesity and its associated complications. Herein, we summarize the currently available evidence regarding the effects of drugs of this class on body adiposity, together with considerations on their potential use as weight loss agents. Furthermore, we attempt to overview their actions and future perspectives of their use with respect to a range of obesity-related disorders, which include cardiovascular, renal, and ovarian dysfunctions, as well as NAFLD and malignancy.

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Introduction For the last few decades obesity has constituted a growing worldwide public health issue that affects the risk and prognosis of several conditions, including cardiovascular disease (CVD), metabolic syndrome (MetS), type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), COVID-19, and cancer.[1-5] According to the World Health Organization data, in 2016 more than 1.9 billion adults were overweight (body mass index [BMI] between 25 and 30 kg/m^2), among whom more than 650 million were obese (BMI >30 kg/m^2).[6] Global trends in T2D parallel those of obesity, and an estimated 422 million individuals were affected as of 2014. The strong causal relationship between these 2 conditions is mediated through the interaction of a variety of genetic and environmental factors that culminate in the development of systemic insulin resistance and eventually β-cell failure; hence the recently coined term "diabesity."[7-9]

As the tide of obesity and its complications is on the rise, there is an urgent need for new drugs with weight-lowering and beneficial metabolic properties.[10] Obesity and obesity-related

disorders, such as MetS, prediabetes, T2D, NAFLD, and CVD complications, as well as the increased prevalence of certain types of cancer make this need more than mandatory. Lifestyle modifications, such as decreased calorie intake and increased physical activity play a key role in combating obesity but are not always very easy to pursue.[11] There are several weight-lowering drugs, mainly lorcaserine, phentermine, topiramate, and glucagon-like peptide-1 (GLP-1) receptor agonists, but their use is restricted by their adverse effects and limited effectiveness. Bariatric surgery offers a more drastic and more lasting weight-lowering potential, and it may reverse prediabetes and T2D in a significant proportion of patients.[10] However, bariatric surgery, while offering the effective solution regarding severe obesity, is also associated with severe adverse effects.[12,13]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a relatively new class of antidiabetic drugs, which act at the level of the renal proximal tubule, causing glucosuria. Apart from the glucosuric effects, they seem to exert pleiotropic biological effects, which are not directly attributable to the reduction of hyperglycemia, such as the reduction of cardiovascular mortality, heart failure (HF) hospitalizations, and hard renal outcomes. This has led to a gradual generalization of the indications for individual SGLT-2 inhibitors outside of the frame of antihyperglycemic therapy or cardiovascular risk reduction among patients with T2D. They are now indicated for patients with HF with preserved (empagliflozin) and reduced ejection fraction (EF) (empagliflozin, dapagliflozin), as well as chronic kidney disease (CKD) of etiology other than diabetic kidney disease, such as ischemic or immunoglobulin A nephropathy, focal segmental glomerulosclerosis, chronic pyelonephritis, and chronic interstitial nephritis (dapagliflozin).[14] Furthermore, their unique mode of action, which results in a glucosuria-induced net caloric loss, renders the agents of these category attractive candidates for obesity therapy.

Very few reviews in the literature have discussed holistically the therapeutic potential of SGLT-2 inhibitors in obesity and its associated complications.[15] In this narrative review, we aim to 1) present the mechanisms of action of SGLT-2 inhibitors, with a special focus on obesity and its associated disorders; 2) appraise their therapeutic applications; 3) discuss adverse effects and tolerability issues, and 4) review potential future perspectives and challenges.

Literature search In August 2022, a literature search of 2 bibliographical databases (MEDLINE and Scopus) was conducted to assess the effects of SGLT-2 inhibitors on obesity. This search used the following terms: "sglt2 inhibitors" and "obesity." The search for the abovementioned terms yielded a total of 697 papers, most of which (539 results) were published between 2017 and 2022 (during the past 5 years). Of these 697 studies, 90 were excluded, as 79 dealt with issues such as chronic kidney disease (n = 20), type 1 diabetes (n = 15), COVID-19 (n = 10), prediabetes (n = 9), dual inhibition of SGLT-1 and SGLT-2 (n = 8), merely heart failure (n = 6), merely hypertension (n = 5), asthma and obstructive sleep apnea (n = 3), or neurological diseases (n = 3), and the remaining 11 studies were not written in English (3 studies in Japanese, 2 in Spanish, 2 in French, 1 in Polish, 1 in Russian, 1 in Swedish, and 1 in Hebrew). In addition, there were 6 books and documents that were excluded, leaving a total of 601 studies included in this search.

Mechanisms of action of sodium-glucose cotransporter-2 inhibitors An important milestone in the course of SGLT-2-inhibition–based therapy was the discovery of the antihyperglycemic effects of phlorizin, a substance isolated from the bark of an apple tree by Josef von Mering in 1886. Although he additionally postulated that the kidneys are its pharmacological target, it was not until the 1970s that inhibition of renal tubular glucose reabsorption was specified as the mechanism of action of phlorizin,[16] while Rossetti et al[17] demonstrated amelioration of insulin resistance and hyperglycemia after phlorizin administration in 1987. The development of the first orally absorbable, phlorizin-derived SGLT-1 and SGLT-2 inhibitor was followed by a rapid discovery of more orally active agents, and in 2013 canagliflozin was the first SGLT-2 inhibitor that received Food and Drug Administration (FDA) approval for the treatment of T2D, followed by dapagliflozin and empagliflozin in 2014.[18] SGLT cotransporters are divided into 2 categories: SGLT-1 and SGLT-2 cotransporters. SGLT-1 cotransporters are mainly located in the small intestine and are responsible for glucose absorption there and for the reabsorption of approximately 10% of the filtered glucose in the upper part of the renal proximal tubule. Their major mechanism of action is to delay glucose absorption in the small intestine, leading to a decrease in the serum postprandial glucose levels.[19] SGLT-1 cotransporters are also located in the kidneys, the brain, the heart, the trachea, the testis, and the prostate gland.[19] On the contrary, SGLT-2 cotransporters are mainly found in the proxy part of the renal proximal tubule, where they act by reabsorbing approximately 90% of the filtered glucose. Apart from the kidneys, SGLT-2 cotransporters are expressed in the brain, the heart, the liver, the thyroid gland, the muscles, and the α pancreatic cells. Their major function in the kidneys is to impede renal glucose reabsorption, causing glucosuria.[20,21]

Apart from lowering serum glucose levels, SGLT-2 inhibitors have been documented to provide significant cardiovascular benefits in patients with T2D. Until now, there are 4 selective SGLT-2 inhibitors with demonstrated cardiovascular benefit: empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin.[22] The abovementioned drugs have been documented to control blood glucose levels, as well as to decrease body weight and

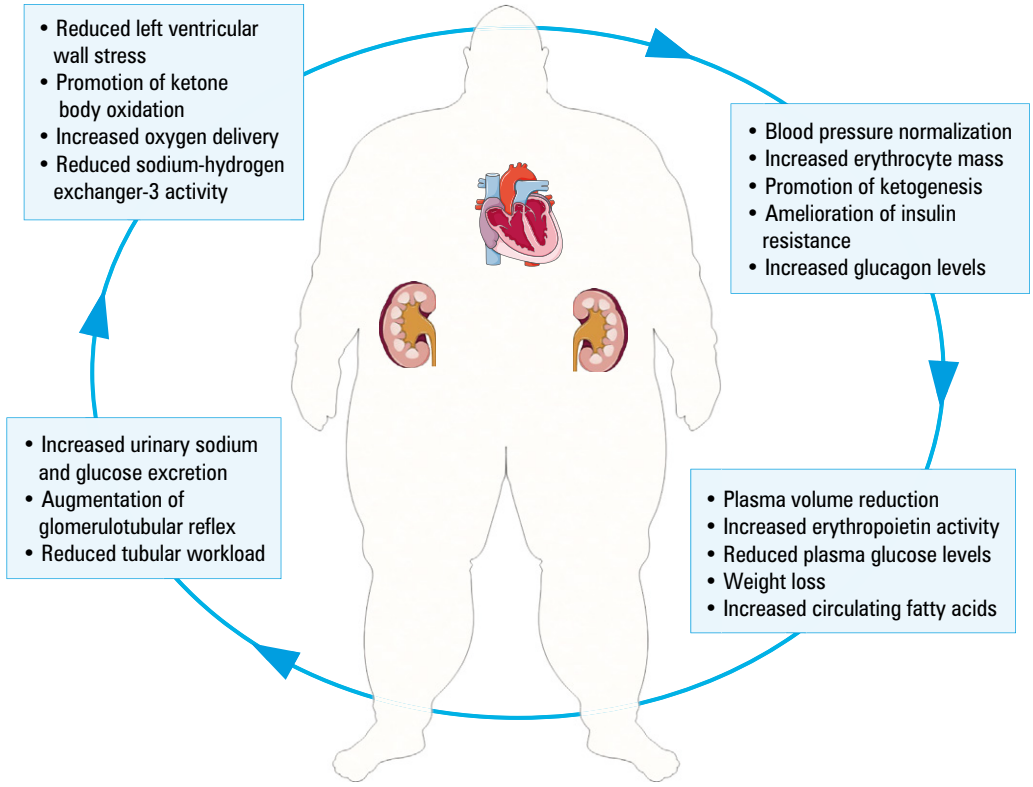

FIGURE 1 Overview of biological actions of sodium-glucose cotransporter-2 inhibitors, which may drive their cardiovascular and renal protective effects based on Braunwald[23] and Tuttle et al[100]

reduce systolic and diastolic blood pressure.[23] FIGURE 1 summarizes the main biological actions of SGLT-2 inhibitors, which are considered to contribute to their cardiorenal protective effects.

Effects on body weight and adiposity indexes SGLT-2 inhibitors cause glucosuria, and thus they alone induce weight loss of approximately 1.5–2 kg. This weight loss phenomenon is dose-dependent and may be maximized, when combining other types of antidiabetic drugs, especially GLP-1 analogs, which suppress appetite by acting directly at the hypothalamus level.[24] Notably, Ferrannini et al[25] demonstrated a disproportionate decrease in body weight induced by SGLT-2 inhibitors used alone due to their glucosuric effects. In particular, SGLT-2 inhibitors produce a smaller weight loss than can be expected based on their glucosuric potential. This discrepancy could be attributed to an increase in energy intake as an adaptive mechanism of the body to prevent any further changes in body weight. According to Ferrannini et al,[25] the human body might have developed an adaptive enhancement in appetite in an effort to induce stability in body weight to counterbalance the weight loss effects of SGLT-2 inhibitors. This notion is also increasingly being supported by other researchers.[24-26] Therefore, the combined use of SGLT-2 inhibitors with drugs suppressing the appetite at the hypothalamus level, such as GLP-1 analogs, is gaining much interest nowadays.[24,27] TABLE 1 presents main studies linking SGLT-2 inhibitors with weight loss among patients with and without T2D. In short, the results from different studies using a wide selection of agents have demonstrated a modest but clinically relevant loss of 0.8 kg under SGLT-2 inhibitor monotherapy, or up to 5.7 kg when SGLT-2 inhibitors were combined with GLP-1 receptor agonists or medications including sulfonylureas. These findings are consistent in patients with and without T2D and are attributable to a net fat mass loss in studies that included measures of body composition estimates, most commonly magnetic resonance tomography. Additionally, the therapy with SGLT-2 inhibitors is well tolerated and adverse events are scarce.

Furthermore, SGLT-2 inhibitors reduce body weight by interfering with excess adipose tissue, which is known to synthesize inflammatory adipocytokines.[28-32] In obesity and obesity-related disorders, such as NAFLD and T2D, adipose tissue macrophages exhibit polarization toward the M1 phenotype, which produces proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6, thus inducing a low-grade inflammatory state.[33,34] On the contrary, the M2 phenotype is restricted in obesity and obesity-related disorders, thereby resulting in mitigation of the anti-inflammatory cytokines, such as IL-4 and IL-10.[35-37] SGLT-2 inhibitors have been documented to reverse the polarization of adipocytes from type 1 macrophages (M1), which release proinflammatory cytokines, to type 2 macrophages (M2), which produce anti-inflammatory cytokines.[24,38] This increase in the M2 phenotype accounts for the beneficial effects of SGLT-2 inhibitors regarding obesity, and is suggested to reduce the chronic inflammatory state, which characterizes and promotes obesity. By bolstering the M2 phenotype, SGLT-2 inhibitors suppress this chronic inflammation, and thus induce weight loss.[36,39]

TABLE 1 List of studies associating overweight/obesity and the effects of sodium-glucose cotransporter-2 inhibitors on body weight among patients with and without type 2 diabetes (continued on the next pages)

Research/year	Population, type of study	Treatment	Main findings	Remarks
List of studies among patients without T2D				
Hussey et al,[S1]a 2010	18 overweight/obese patients without T2D; A double-blind, placebo-controlled, randomized, phase 1 trial	I) Sergliflozin etabonate 500 mg/tid II) Sergliflozin etabonate 1000 mg/tid III) Placebo	Sergliflozin induced significant weight loss of approximately 1.55 kg for sergluflozin 500 mg/tid to 1.74 kg for sergluflozin 1000 mg/tid, from baseline after 15 days of administration	Sergluflozin was generally well tolerated; No major adverse effects reported
Bays et al,[54] 2014	376 overweight/obese patients without T2D; A double-blind, placebo-controlled, phase 2b trial	I) Canagliflozin 50 mg II) Canagliflozin 100 mg III) Canagliflozin 300 mg IV) Placebo	↓ body weight by I) 2.2% II) 2.9% III) 2.7% IV) 1.3%	Canagliflozin ↓ body weight without any severe adverse effects
Napolitano et al,[S2] 2014	30 overweight/obese patients without T2D; A double-blind, placebo-controlled, randomized, pilot trial	I) Sergliflozin etabonate 1000 mg/tid II) Remogliflozin etabonate 250 mg/tid III) Placebo	No changes in body weight reported in the 3 groups; All patients except 1 exhibited weight loss	↓ in the leptin/adiponectin ratio in the groups receiving sergliflozin or remogliflozin when compared with placebo
Lundkvist et al,[S3] 2017a	50 obese patients without T2D; A randomized, placebo-controlled, phase 2a trial	I) Dapagliflozin 10 mg/d + exanetide 2 mg sc every week for 24 weeks II) Placebo	↓ body weight by 4.13 kg (SD) (95% CI, 6.44–1.81 kg; P <0.001); ↓ in total adipose tissue by 3.8 l	36% of the patients enrolled lost ≥5% of their body weight; The loss in body weight was attributed to ↓ in adipose tissue with no ↓ in lean tissue, as estimated by MRI
Lundkvist et al,[S4] 2017b	50 obese adults without T2D; Open-label extension trial	I) Dapagliflozin 10 mg/d + exanetide 2 mg sc every week for 1 year II) Placebo	↓ body weight by 5.7 kg; ↓ in total adipose tissue by 5.3 l	↓ body weight lasting for 1 year; ↓ in adipose tissue, as estimated by MRI
Hollander et al,[S5] 2017	335 overweight/obese patients without T2D; A double-blind, placebo-controlled, phase 2a trial	I) Canagliflozin 300 mg/d II) Phentermine 15 mg/d III) Canagliflozin 300 mg/d + phentermine 15 mg/d IV) Placebo	↓ body weight by 6.9% [95% CI, 8.6%–5.2%], P <0.001 in the combination group	↓ body weight ≥5%, without any severe adverse effects
Ramirez-Rodriguez et al,[S6] 2020	24 patients with prediabetes; A double-blind, placebo-controlled, randomized trial	I) Dapagliflozin 10 mg/d II) Placebo	↓ body weight by 3.0 kg or 3.7% vs 1 kg in placebo (P = 0.019)	↓ body weight; ↓ BMI; ↓ WC
Faecher et al,[S7] 2021	120 overweight/obese patients with prediabetes; A controlled, randomized, parallel-arm, non-blind, open label trial	I) Metformin 1700 mg/d II) Dapagliflozin 10 mg/d III) Placebo IV) Exercise group	Dapagliflozin and exercise led to small improvements in glycemic control among patients with prediabetes, when compared with metformin and placebo	The study revealed uncertainty about glycemic control in prediabetic patients; The study did not mention any differences in body weight between the groups
List of studies in patients with T2D				
Ferrannini et al[S8], 2010	485 patients with T2D; A double-blind, placebo-controlled randomized, phase 3 trial	I) Dapagliflozin 2.5 mg/d II) Dapagliflozin 5 mg/d III) Dapagliflozin 10 mg/d IV) Placebo	↓ in mean HbA_{1c} of 0.58%, 0.77%, 0.89% in group I, II, and III, respectively, P <0.0005; ↓ in mean HbA_{1c} of 0.23% in the placebo group	No severe adverse effects reported; Noninsulin-dependent mode of action

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Research/year	Population, type of study	Treatment	Main findings	Remarks
Strojek et al,[S9] 2011	597 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Dapagliflozin 2.5 mg/d + glimepiride 4 mg/d II) Dapagliflozin 5 mg/d + glimepiride 4 mg/d III) Dapagliflozin 10 mg/d + glimepiride 4 mg/d IV) Placebo + glimepiride 4 mg/d	↓ in mean HbA_{1c} of 0.58%, 0.63% and 0.82% in group I, II, and III, respectively, $P < 0.0001$	Dapagliflozin as an addition to therapy with glimepiride ⇊ HbA_{1c} and TBW; ↑ in hypoglycemia reported
Nauck et al,[S10] 2011	814 patients with T2D; A double-blind, placebo-controlled, randomized noninferiority, phase 3 trial, lasting for 1 year	I) Metformin 1500–2500 mg/d + dapagliflozin 5–10 mg/d II) Metformin 1500–2500 mg/d+ glipizide 10–20 mg/d	↓ in mean HbA_{1c} of 0.52%, for both dapagliflozin and glipizide; Weight loss of 3.2 kg vs weight gain of 1.2 kg for glipizide, $P < 0.0001$	↓ in body weight of ≥5% in 33.33% of the patients on dapagliflozin; ↑ infections of the genitalia and UTIs on dapagliflozin ↑ of hypoglycemia on glipizide
Bailey et al,[S11] 2012	282 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Dapagliflozin 1 mg/d II) Dapagliflozin 2.5 mg/d III) Dapagliflozin 5 mg/d IV) Placebo	↓ in mean HbA_{1c} of 0.68%, 0.72%, and 0.82%, in group I, II, and III, respectively, $P < 0.0001$	Insulin-independent mode of action; No severe adverse effects reported
Bolinder et al,[S12] 2012	182 patients with T2D; A double-blind, placebo-controlled, randomized trial	I) Dapagliflozin 10 mg/d + metformin II) Placebo + metformin	↓ TBW of 2.08 kg (95% CI, 2.84–1.31 kg; $P < 0.0001$)	Dapagliflozin further ↓ TBW, ↓ of FM, VAT, and SAT
Bailey et al,[S13] 2013	546 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Dapagliflozin 2.5 mg/d + metformin ≥1500 mg/d II) Dapagliflozin 5 mg/d + metformin ≥1500 mg/d III) Dapagliflozin 10 mg/d + metformin ≥1500 mg/d IV) Placebo + metformin ≥1500 mg/d	↓ in mean HbA_{1c} of 0.48%, 0.58%, and 0.78% in group I, II, and III, respectively, $P < 0.0008$; ↑ in mean HbA_{1c} of 0.02% in the placebo group	Dapagliflozin as an addition to the therapy with metformin ⇊ HbA_{1c} and TBW; No severe adverse effects reported
Lambers Heerspink et al,[S14] 2013	75 patients with T2D; A double-blind, placebo-controlled, randomized, phase 2 trial	I) Dapagliflozin 10 mg/d II) Hydrochlorothiazide 25 mg/d III) Placebo	↓ body weight 2.4 kg vs 0.1 kg in the placebo group	Dapagliflozin and hydrochlorothiazide ↓ body weight; Comparison of the diuretic and blood pressure lowering effects of dapagliflozin and hydrochlorothiazide
Kaku et al,[S15] 2014	261 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Dapagliflozin 5 mg/d II) Dapagliflozin 10 mg/d III) Placebo	↓ in mean HbA_{1c} of 0.41% and 0.45% in group I and II, respectively	Dapagliflozin ⇊ HbA_{1c} and TBW; Hypoglycemia only in 2 patients on dapagliflozin 10 mg/d
Ji et al,[S16] 2014	393 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Dapagliflozin 5 mg/d II) Dapagliflozin 10 mg/d III) Placebo	↓ in mean HbA_{1c} of 1.04% and 1.11% in group I and II, respectively, $P < 0.0001$	Dapagliflozin ⇊ HbA_{1c} and TBW; Infrequent hypoglycemia
Nauck et al,[S17] 2014	814 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial, lasting for 2 years	I) Metformin 1500–2500 mg/d + dapagliflozin 5–10 mg/d II) Metformin 1500–2500 mg/d + glipizide 10–20 mg/d	↓ in body weight of 5.1 kg (95% CI, 5.7–4.4 kg) after 2 years	↓ in body weight and ↑ glycemic durability that lasted longer on dapagliflozin than on glipizide; Hypoglycemia much (10-fold) less frequent on dapagliflozin than on glipizide; Genital infections and UTIs more frequent on dapagliflozin than on glipizide

TABLE 1 List of studies associating overweight/obesity and the effects of sodium-glucose cotransporter-2 inhibitors on body weight among patients with and without type 2 diabetes (continued on the next pages)

Research/year	Population, type of study	Treatment	Main findings	Remarks
Jabbour et al,[S18] 2014	432 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Sitagliptin 100 mg/d ± metformin ≥1500 mg/d + dapagliflozin 10 mg/d II) Sitagliptin 100 mg/d ± metformin ≥1500 mg/d + placebo	↓ in body weight of 2.3 kg on dapagliflozin vs 0.3 kg on placebo	↓ in body weight and HbA_{1c} on dapagliflozin vs placebo; Genital infections more frequent on dapagliflozin, UTI frequency almost the same on dapagliflozin and placebo
Kovacs et al,[S19] 2014	498 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Pioglitazone ≥30 mg/d ± metformin ≥1500 mg/d + empagliflozin 10 mg/d II) Pioglitazone ≥30 mg/d ± metformin ≥1500 mg/d + empagliflozin 25 mg/d III) Pioglitazone ≥30 mg/d ± metformin ≥1500 mg/d + placebo	↓ in mean body weight (SD) of 1.62 kg (0.21) and 1.47 kg (0.21) on empagliflozin 10 mg and 25 mg, respectively, vs weight gain of 0.34 kg (0.21) on placebo (both $P < 0.001$)	Empagliflozin 10 mg/d or 25 mg/d resulted in ↓ in both body weight and HbA_{1c}; Empagliflozin generally well tolerated
Strojek et al,[S20] 2014	597 patients with T2D; A double-blind, parallel-group, randomized, phase 3 trial	I) Glimepiride 4 mg/d II) Glimepiride 4 mg/d + dapagliflozin 2.5 mg/d III) Glimepiride 4 mg/d + dapagliflozin 5 mg/d IV) Glimepiride 4 mg/d + dapagliflozin 10 mg/d	No significant changes in mean HbA_{1c} were observed; ↓ in body weight of 1.36 kg, 1.54 kg, and 2.41 kg reported on dapagliflozin 2.5 mg/d, 5 mg/d, and 10 mg/d, respectively, over 48 weeks	Addition of dapagliflozin led to sustained weight loss; No severe adverse effects reported
Bolinder et al,[S21] 2014	182 patients with T2D; A double-blind, placebo-controlled, randomized, multi-arm, parallel-group, phase 3 trial	I) Metformin ≥1500 mg/d II) Metformin ≥1500 mg/d + dapagliflozin 10 mg/d	↓ in mean HbA_{1c}; ⇊ in body weight of 4.54 kg and ↓ in WC of 5 cm	⇊ in body weight and ⇊ in FM of 2.8 kg; No severe adverse effects reported
DeFronzo et al,[S22] 2015	674 patients with T2D; A double-blind, parallel-group, randomized, phase 3 trial	I) Metformin ≥1500 mg/d + linagliptin 5 mg/d II) Metformin ≥1500 mg/d + empagliflozin 10 mg/d III) Metformin ≥1500 mg/d + empagliflozin 25 mg/d IV) Metformin ≥1500 mg/d + linagliptin 5 mg/d + empagliflozin 10 mg/d V) Metformin ≥1500 mg/d + linagliptin 5 mg/d + empagliflozin 25 mg/d	⇊ in body weight and HbA_{1c}	No severe adverse effects reported attributable to the use of empagliflozin; Allergic reactions in 3 patients occurred when linagliptin was used alone or in combination with empagliflozin
Del Prato et al,[S23] 2015	814 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Metformin ≥1500 mg/d + glipizide 10–20 mg/d II) Metformin ≥1500 mg/d + dapagliflozin up to 20 mg/d	↓ in mean HbA_{1c} and ⇊ in TBW of 4.38 kg (95% CI, 5.31–3.46 kg), when comparing dapagliflozin with glipizide at 4 years	⇊ in mean HbA_{1c} and TBW at 4 years on dapagliflozin vs glipizide; Genital infections and UTIs more frequent on dapagliflozin but tended to disappear with time and antibiotics
Bailey et al,[S24] 2015	274 patients with T2D; A double-blind, placebo-controlled, parallel-group, phase 3 trial	I) Placebo, ie patients who after completion of 24 weeks of the study received metformin 500 mg/d (low dose), therefore: II) Metformin 500 mg/d + dapagliflozin 2.5 mg/d III) Metformin 500 mg/d + dapagliflozin 10 mg/d IV) Metformin 500 mg/d + dapagliflozin 10 mg/d	↓ in mean HbA_{1c} and ⇊ in TBW of 2.016 kg, $P = 0.016$	⇊ in mean HbA_{1c} and TBW at 2 years on dapagliflozin vs low-dose metformin; Genital infections and UTIs more frequent on dapagliflozin; Hypoglycemia uncommon on dapagliflozin

TABLE 1 List of studies associating overweight/obesity and the effects of sodium-glucose cotransporter-2 inhibitors on body weight among patients with and without type 2 diabetes (continued on the next page)

Research/year	Population, type of study	Treatment	Main findings	Remarks
Rosenstock et al,[S25] 2015	534 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Metformin ≥1500 mg/d + saxagliptin 5 mg/d + placebo II) Metformin ≥1500 mg/d + dapagliflozin 10 mg/d + placebo III) Metformin ≥1500 mg/d + saxagliptin 5 mg/d + dapagliflozin 10 mg/d	⇊ in mean HbA_{1c} and ⇊ in body weight in patients on saxagliptin + dapagliflozin apart from metformin	Triple combination of metformin + dapagliflozin + saxagliptin resulted in ⇊ in HbA_{1c} and ⇊ in body weight; No episodes of severe hypoglycemia reported with the triple combination
Fulcher et al,[S26] 2016	411 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) DPP-4 inhibitor + placebo II) DPP-4 inhibitor + canagliflozin 100 mg/d III) DPP-4 inhibitor + canagliflozin 300 mg/d IV) GLP-1 analog + placebo V) GLP-2 analog + canagliflozin 100 mg/d VI) GLP-1 analog + canagliflozin 300 mg/d	↓ in mean HbA_{1c} and ↓ in body weight with canagliflozin 100 mg/d or 300 mg/d	In the patients receiving incretin mimetics, canagliflozin 100 mg/d or 300 mg/d ↓ body weight; Incidence of hypoglycemia ↑ with canagliflozin addition
Frias et al,[S27] 2016	695 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Metformin ≥1500 mg/d + exanetide 2 mg/weekly II) Metformin ≥1500 mg/d + dapagliflozin 10 mg/d III) Metformin ≥1500 mg/d + exanetide 2 mg/weekly + dapagliflozin 10 mg/d	↓ in mean HbA_{1c} and body weight on the combination of exanetide + dapagliflozin	As expected, exanetide + dapagliflozin were superior regarding lowering mean HbA_{1c} and weight loss, and more patients with weight loss ≥5% of their body weight; No major adverse effects reported
Mathieu et al,[S28] 2016	294 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Metformin + saxagliptin + placebo II) Metformin + saxagliptin + dapagliflozin 10 mg/d	HbA_{1c}, –0.74% vs 0.07%; FPG, –27 mg/dl vs 10 mg/dl; body weight, –2.1 kg vs –0.4 kg on dapaglifozin vs placebo	Triple combination of metformin + dapagliflozin + saxagliptin resulted in ⇊ in mean HbA_{1c} and ⇊ in body weight; Overall, the triple combination was well tolerated and provided sustainable effects; Only genital infections with *Candida* species were more common in the dapagliflozin group
Neal et al,[58] 2017	10 142 patients with T2D and high CVD risk receiving standard care; A double-blind, placebo-controlled, randomized, phase 3 trial (CANVAS program)	I) Canagliflozin 100 mg/d II) Canagliflozin 300 mg/d III) Placebo	Body weight loss of 1.46 kg	↓ risk of CVD event; ↑ risk of lower limb amputation
Wanner et al,[S29] 2018	7020 patients with T2D and CVD receiving standard care; A double-blind, placebo-controlled, randomized, phase 3 trial (EMPAREG--OUTCOME trial)	I) Empagliflozin 10 mg/d II) Empagliflozin 25 mg/d III) Placebo	Body weight loss of 2 kg	Empagliflozin addition to standard care led to ↓ in body weight; No severe adverse effects reported
Ludvik et al,[S30] 2018	424 patients with T2D; A double-blind, placebo-controlled, parallel--arm, randomized, phase 3b trial	I) SGLT-2 inhibitor + placebo II) SGLT-2 inhibitor + dulaglutide 0.75 mg/weekly III) SGLT-2 inhibitor + dulaglutide 1.5 mg/weekly	Patients on dulaglutide instead of placebo had ⇊ in mean HbA_{1c} and ⇊ body weight	Although the addition of dulaglutide to SGLT-2 inhibitor resulted in significant ⇊ in body weight, adverse side effects were more frequent in the groups that received dulaglutide; Nausea, diarrhea, vomiting were more frequent in patients on dulaglutide instead of placebo

TABLE 1 List of studies associating overweight/obesity and the effects of sodium-glucose cotransporter-2 inhibitors on body weight among patients with and without type 2 diabetes (continued from the previous pages)

Research/year	Population, type of study	Treatment	Main findings	Remarks
Pratley et al,[S31] 2018	1233 patients with T2D; A double-blind, placebo-controlled, randomized, phase 3 trial	I) Metformin ≥1500 mg/d + ertugliflozin 5 mg/d II) Metformin ≥1500 mg/d + ertugliflozin 15 mg/d III) Metformin ≥1500 mg/d + ertugliflozin 5 mg/d + sitagliptin 100 mg/d IV) Metformin ≥1500 mg/d + ertugliflozin 15 mg/d + sitagliptin 100 mg/d V) Metformin ≥1500 mg/d + sitagliptin 100 mg/d	↓ in mean HbA_{1c} and ↓ in body weight with the combination of ertugliflozin + sitagliptin, when compared with sitagliptin alone	↓ in glucose levels and body weight after 52 weeks of observation; Only genital infections with *Candida* species more common in patients on ertugliflozin
Perkovic et al,[90] 2019	4401 patients with T2D and albuminuric CKD; A double-blind, placebo-controlled, randomized, phase 3 trial (CREDENCE trial)	I) Canagliflozin 100 mg/d II) Placebo	Canagliflozin induced weight loss of 0.8 kg	Canagliflozin ⇊ the risk of CVD events and renal failure, ↓ body weight; No differences in the risk of amputations
Wiviott et al,[57] 2019	17 160 patients with T2D receiving standard care; A double-blind, placebo-controlled, randomized, phase 3 trial (DECLARE-TIMI 58)	I) Dapagliflozin 10 mg II) Placebo	Weight loss of 1.8 kg	Dapagliflozin as an additional treatment to standard care was associated with ⇊ risk of CVD events and ⇊ risk of renal events; DKA more common on dapagliflozin when compared with placebo (0.3% vs 0.1%, $P = 0.02$); Genital infections more common on dapagliflozin
Cannon et al,[S32] 2020	8246 patients with T2D and atherosclerotic CVD receiving standard care; A double-blind, placebo-controlled, randomized, phase 3 trial (VERTIS CV)	I) Ertugliflozin 5 mg/d II) Ertugliflozin 15 mg/d III) Placebo	Weight loss of 2.4 kg on ertugliflozin 5 mg/d and 2.8 kg on ertugliflozin 15 mg/d	Ertugliflozin was not inferior to placebo regarding CVD risk; Amputations performed in 2% of patients on ertugliflozin 5 mg/d and in 2.1% of patients on ertugliflozin 15 mg/d, vs 1.6% in the placebo group

[a] References *S1–S32* are listed in Supplementary material

Abbreviations: ↓, decrease; ⇊, strong decrease; ↑, increase; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FM, fat mass; HbA_{1c}, glycated hemoglobin; MRI, magnetic resonance imaging; RCT, randomized controlled trials; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes mellitus; TBW, total body weight; tid, thrice daily; UTIs, urinary tract infections; VAT, visceral adipose tissue; WC, waist circumference

In addition, it is widely known that brown adipose tissue (BAT) plays a key role in obesity and obesity-related disorders. More specifically, browning of the white adipose tissue (WAT) has been suggested to be a crucial factor in combating obesity.[40-43] This is mainly achieved by increasing energy expenditure by means of increased expression of uncoupling protein 1 (UCP-1) in BAT, as well as an enhancement of cells expressing UCP-1 in WAT. These brown-like adipocytes, often called beige cells, are characterized by an increased expression of UCP-1, and thus by their transformation into brown adipocytes.[39] SGLT-2 inhibitors have been documented to increase body energy expenditure by increasing the expression of UCP-1 in WAT and BAT, leading to browning of the adipose tissue. In this process, adiponectin and fibroblast growth factor 21 have been found to be elevated as a result of chronic administration of SGLT-2 inhibitors.[44-48]

Overall, SGLT-2 inhibitors seem to be associated with weight loss via their glucosuric effects, polarization toward the M2 phenotype of macrophages, and browning of the WAT.

Effects on glycemic control SGLT-2 inhibitors induce glucosuria, thereby ameliorating the serum glucose levels, while their ability to promote fat utilization and browning of the WAT improves insulin sensitivity.[24] SGLT-2 inhibitors used as monotherapy have been shown to lower fasting plasma glucose (FPG) by 20–46 mg/dl and glycated hemoglobin (HbA_{1c}) by 0.54% to 1.45% in patients with baseline HbA_{1c} of 7% to 9.1%, as compared with placebo. Notably, the addition of SGLT-2 inhibitors as an add-on therapy to metformin may lower FPG by 15–40 mg/dl and HbA_{1c} by 0.54%–0.77% as compared with placebo in patients with baseline HbA_{1c} between 7.9% and 8.2%.[49]

Although SGLT-2 inhibitors are widely used for the treatment of patients with T2D, individuals with T1D may also benefit from their pleiotropic properties, apart from the glucose lowering effects.[49-51] In fact, sotagliflozin, a dual SGLT-1 and SGLT-2 inhibitor, is authorized in the European Union only for the treatment of patients with both T1D and obesity.[52] However, the use of SGLT-2 inhibitors or even sotagliflozin among patients with T1D has been associated with higher rates of euglycemic diabetic ketoacidosis (EDKA), as these patients are more prone to ketoacidosis than patients with T2D. Besides, there is always a higher risk of hypoglycemia among patients with T1D due to the concurrent use of insulin.[53]

Regarding the effects of SGLT-2 inhibitors on lipid parameters, it has been suggested that this class of antidiabetic drugs may lead to a small increase in serum high-density lipoprotein cholesterol levels, whereas other reports have also shown a slight increase in low-density lipoprotein cholesterol levels.[10,54] As these drugs are now extensively used, more research in terms of their effects on lipid metabolism and biomarkers will most probably appear in the near future.

Cardiovascular effects Despite the fact that SGLT-2 inhibitors have been mainly introduced for the treatment of patients with T2D, they possess pleiotropic properties over and beyond their antidiabetic potential.[49] Among these pleiotropic effects, their cardioprotective ability is of the utmost importance. In particular, the EMPA-REG OUTCOME study[55] was the first to show a significant decrease in the rate of death from CVD causes, nonfatal infarction, or nonfatal stroke among 7020 patients with T2D at high risk of an adverse CVD effect. The CANVAS study[56] followed, which enrolled 10 142 patients with T2D and high CVD risk, and confirmed a lower risk of the same adverse CVD effects. The DECLARE--TIMI 58 study,[57] also published, like prior trials, in *New England Journal of Medicine*, has documented a significant reduction in the rate of hospitalization due to HF among 10 186 patients with T2D and lowered risk of atherosclerotic CVD in the patients followed for a median of 4.2 years.

Furthermore, the EMPEROR-Reduced study,[58] which enrolled 3730 patients with HF and the latest EMPEROR-Preserved study,[59] which investigated 5988 patients with HF, have shown beneficial cardiovascular effects associated with the use of empagliflozin. In particular, a significant decrease in death or hospitalization rate due to HF was noted in both studies, regardless of the presence of T2D. The DAPA-HF study[60] including 4744 patients with HF and reduced EF has also confirmed the abovementioned findings for dapagliflozin.

These remarkable cardioprotective effects of SGLT-2 inhibitors have led to their use in patients even without T2D but with established HF. Regarding their beneficial effects in patients with HF, these may be attributed to the increased production of ketones by SGLT-2 inhibitors, which, in turn, ameliorate mitochondrial dysfunction observed in HF and increase adenosine triphosphate production, resulting in an improved ventricular contractility.[23] In particular, SGLT-2 inhibitors may lead to changes in intracellular sodium and calcium concentrations, resulting in improved ventricular contractility and fewer cardiac arrhythmias.[23] In addition, cardiac inflammation and the subsequent cardiac fibrosis are attenuated by the use of SGLT-2 inhibitors. This effect is mainly attributed to decreased production of free radicals in the cardiomyocytes, as these antidiabetic drugs induce an antioxidative and anti-inflammatory milieu that supports coronary endothelial function. It is also important to highlight that the epicardial fat surrounding the heart, characterized by increased production of proinflammatory cytokines, is decreased following the use of SGLT-2 inhibitors, thus resulting in a reduction of proinflammatory cytokines and amelioration of the surrounding environment.[61] Besides, due to the weight loss induced by

SGLT-2 inhibitors, there is also a general decrease in the production of proinflammatory cytokines by the adipose tissue, which accounts for a better and more functional cardiac microenvironment.[62]

Effects on arterial blood pressure Due to their natriuretic effects, SGLT-2 inhibitors slightly reduce arterial blood pressure (3–7 mm Hg for systolic and 2 mm Hg for diastolic blood pressure).[63] This antihypertensive potential is reported to be present regardless of the use of other antihypertensive drugs, such as loop diuretics. However, it has been demonstrated that SGLT-2 inhibitors and loop diuretics may share a synergistic natriuretic effect.[64] Notably, the antihypertensive potential of SGLT-2 inhibitors does not induce further release of renin by the macula densa. The decreased intravascular volume resulting from the natriuretic properties of SGLT-2 inhibitors does not seem to activate the renin-angiotensin-aldosterone system or the sympathetic activity tone. This unique feature of SGLT-2 inhibitors may be the cornerstone of the beneficial effects of SGLT-2 inhibitors regarding blood pressure.[64] Apart from their natriuretic effect, SGLT-2 inhibitors decrease the arterial stiffness, thus reducing the arterial tone and decreasing the arterial blood pressure. This decrease in arterial stiffness may be attributed to reduction in the perivascular fat caused by SGLT-2 inhibitors, as reported by Batzias et al[65] in their meta-analysis. Furthermore, the weight loss effect may also account for the reduction in arterial blood pressure.[65] Overall, the natriuretic effects together with the weight loss and the reduction in arterial stiffness all result in decreased arterial blood pressure.

Effects on renal function Among patients with T2D, the increased reabsorption of sodium and glucose by the SGLT-2 cotransporters accounts for the state of hyperfiltration noted in the very early stages of diabetic kidney disease.[10] This phenomenon is mainly attributed to an enhanced reabsorption of sodium leading to vasoconstriction of the afferent arteriole. The use of SGLT-2 inhibitors may result in reduced hyperfiltration as well as lowered intraglomerular pressure, and therefore ameliorated renal function. Interestingly, in the EMPA-REG Outcome study,[55] the administration of empagliflozin was associated with a reduction in the rate of doubling of serum creatinine levels, a reduction in albuminuria, progression to end-stage renal disease (ESRD), and death related to kidney dysfunction. The EMPA-REG Outcome study[55] was the first to report these favorable renal effects associated with the use of a SGLT-2 inhibitor. The CANVAS trial ensued,[66] which confirmed that the use of another SGLT-2 inhibitor, canagliflozin, resulted in reduction in the progression of albuminuria and a 40% decline in deterioration of estimated glomerular filtration rate (eGFR), the need for renal replacement treatment, and death of renal origin causes. The CREDENCE study[67] was the first one investigating the use of canagliflozin with kidney function as a primary end point. This trial showed that the relative risk of death from renal causes among the enrolled 4401 patients was reduced by 34%, while the relative risk of ESRD was reduced by 32% during the median follow-up of 2.62 years.[68] The DAPA-CKD study,[69] which dealt with the administration of another SGLT-2 inhibitor, dapagliflozin, in 4304 patients with kidney dysfunction and with or without T2D, has also demonstrated a slower decline in eGFR in the long term, especially among patients with higher HbA_{1c} and higher urinary to creatinine ratio at the beginning of the study. The consistent results demonstrating a reduction of adverse renal outcomes across a broad selection of different SGLT-2 inhibitors point toward a class renoprotective effect of SGLT-2 inhibitors. Therefore, the usage of SGLT-2 inhibitors has been expanded even in lower eGFR, where their antidiabetic potential is compromised but their nephroprotective as well as cardioprotective properties are still sustained. In particular, at GFR below 45 ml/min/1.73 m^2, SGLT-2 inhibitors have lower glycemic efficacy and usually another agent should be added to achieve glycemic goals. However, depending on the labeling of representative drugs, they should be initiated even when eGFR is between 30 and 45 ml/min/1.73 m^2 due to their dual beneficial cardiorenal effects. The results of DAPA-CKD study[7] generalized these findings outside of the frame of diabetic nephropathy, and led to approvals by the FDA and the European Medicines Agency, regarding the use of dapagliflozin among patients with CKD of nondiabetic etiology.

Regarding CKD and the obesity paradox, it should be noted that the phenomenon of "reverse epidemiology" is observed in CKD patients, whereas increased BMI has been associated with better survival outcomes.[70] However, this phenomenon, which apart from CKD has been observed in heart disease, liver cirrhosis, and chronic obstructive lung disease, may be attributed to protein wasting and cachexia, which characterize the advanced stages of the abovementioned disorders.[70] SGLT-2 inhibitors act mainly by causing glucosuria and natriuresis, thereby inducing weight loss without leading to sarcopenia and cachexia.[71] In addition, it should be pointed out that SGLT-2 inhibitors, by interfering with the inflammasome pathway, may result in reduced release of IL-1β, which is widely known for its key role in the pathogenesis of CKD.[72]

Effects on hepatic function and nonalcoholic fatty liver disease Nowadays, NAFLD has been assessed to affect almost 70% to 80% of patients with T2D,[73,74] while in obesity its prevalence ranges from 50% to 90%, depending on the degree of excess adiposity.[76] NAFLD, which is characterized by excess fat accumulation in the hepatocytes, may be associated with nonalcoholic steatohepatitis (NASH), cirrhosis, and even hepatocellular carcinoma.[76,77] Apart from these severe

liver consequences, NAFLD, especially in patients with obesity and T2D, calls for action in terms of CVD, as it is related to increased cardiovascular adverse effects.[78,79] In their recent meta-analysis, Mantovani et al[80] have concluded that SGLT-2 inhibitors have beneficial effects regarding NAFLD. In particular, they have documented a significant decrease in liver fat content as estimated by magnetic resonance techniques as well as reductions in liver enzymes, such as alanine aminotransferase (ALT) and gamma-glutamyl-transferase (γ-GT). Their meta-analysis included randomized controlled trials (RCTs) involving the use of empagliflozin, dapagliflozin, canagliflozin, and ipragliflozin in patients with NAFLD defined by magnetic resonance techniques and not by liver biopsy, as there were no eligible RCTs regarding SGLT-2 inhibitors and NAFLD assessed by liver biopsy. The participants in the included studies were overweight or obese and 90% had T2D. When compared with the placebo group, the use of SGLT-2 inhibitors for 24 weeks resulted in amelioration of serum ALT and γ-GT levels as well as improvement in liver fat content (pooled weighted mean differences, −2.05%; 95% CI, −2.61% to −1.48%), and reduction in body weight of approximately 3.5 kg.[80] Overall, evidence points toward a beneficial class effect of SGLT-2 inhibitors in liver steatosis among patients with T2D. More studies in the field are needed to generalize the current findings in patients without overt dysglycemia. Additionally, in order to assess potential synergistic effects of SGLT-2 inhibition and other treatment approaches, at least 1 ongoing study aims to compare the effects of combined SGLT-2 inhibitor (empagliflozin 10 mg) and GLP-1 agonist (1 mg semaglutide weekly) vs empagliflozin monotherapy or placebo in NASH among T2D patients, with invasive (liver biopsy) and noninvasive (elastography) measures to asses liver steatosis, fibrosis, and inflammation (clinicaltrials.gov registration number: NCT04639414)

Effects on ovarian function Polycystic ovary syndrome (PCOS) affects approximately 20% of women of reproductive age.[28] It is characterized by abnormalities in ovulation, hyperandrogenemia, and / or pathologic ovarian ultrasound morphology, and may be associated with insulin resistance and subsequent hyperinsulinemia. The latter feature is responsible for the metabolic derangement related to PCOS and the increased CVD risk. In this case, insulin sensitizers, such as metformin or thiazolidinediones may be alternatives to oral contraceptives.[81] Approximately 60% to 70% of women with PCOS finally develop insulin resistance and hyperinsulinemia. The use of other antidiabetic agents, especially with weight-lowering effects is also under investigation regarding the treatment options for women with PCOS. Despite the lack of SGLT-2 cotransporters in the ovaries, the effects of SGLT-2 inhibitors, which induce glucosuria leading to weight loss and natriuresis resulting in reduction of blood pressure, are among the most beneficial features regarding their use in women with PCOS.[81] Notably, 1 current RCT studying the administration of 25 mg of empagliflozin or 1500 mg of metformin in 39 women with PCOS, has showed a reduction in body weight, BMI, waist circumference, and total fat, but no significant differences in insulin resistance and androgen levels.[82] Another RCT is ongoing regarding the administration of canagliflozin vs metformin among women with PCOS [NCT04700839]. Overall, due to the weight loss and blood pressure lowering effects of SGLT-2 inhibitors, there is an ongoing interest in the administration of SGLT-2 inhibitors in women with PCOS to also improve various CVD risk parameters.

Adverse events and tolerability The most common adverse effect of SGLT-2 inhibitors is genital candidiasis. The phenomenon of glucosuria, which is the main mechanism of action in this category of drugs, confers a favorable environment for the growth of *Candida* species. Apart from mycotic genitalia infections, which are reported to be 4 to 6 times increased, bacterial infections of the urinary system may also develop, although less frequently. These urinary tract infections are rarely severe enough to cause pyelonephritis.[83,84] Another adverse effect of this class of drugs is that they may provoke EDKA, which, however, is highly preventable and may be managed by discontinuation of the drug and intravenous administration of fluids together with insulin and potassium supplementation, if needed. Nevertheless, if a patient is adequately hydrated, this adverse effect occurs very rarely.[23,85] A transient increase in serum creatinine levels, albeit of questionable clinical relevance, is observed frequently following the initiation of SGLT-2 inhibitor therapy.[86] This is in contrast with documented long-term nephroprotective effects of SGLT-2 inhibitors (see section *Effects on renal function*), while therapy with dapagliflozin appears to be safe even in patients with stage 4 CKD.[87] Regarding canagliflozin, the CANVAS study[56] reported that canagliflozin therapy was associated with an increased risk of limb amputation and bone fractures. However, these results were not confirmed in the CREDENCE study,[88] while they have not been reported with the use of other SGLT-2 inhibitors. Furthermore, a therapy with SGLT-2 inhibitors does not seem to increase fracture risk in patients with CKD, regardless of baseline eGFR.[89]

Perspectives and challenges According to the American Diabetes Association and the American Heart Association recommendations for 2022, in patients with T2D and established CVD or renal disease, SGLT-2 inhibitors or GLP-1 analogs or both are recommended.[23,90,91] Regarding obesity treatment, despite the fact that SGLT-2 inhibitors induce weight loss, their weight-lowering effects are counterbalanced by an increased appetite

and calorie intake. Therefore, they are not probable to be used alone in obesity treatment. However, their combination with drugs suppressing appetite and/or inducing satiety would be much more feasible and welcome. Indeed, a combination of a SGLT-2 inhibitor with a GLP-1 analog, especially a once-weekly administered GLP-1 analog, would be more convenient and more potent in this regard. In addition, it would be interesting to combine a SGLT-2 inhibitor with a dual GLP-1 analog and glucose-dependent insulinotropic polypeptide, which may be even more efficient in suppressing appetite and in promoting reduced gastric emptying. Regarding the already used weight-lowering drugs, such as lorcaserine, GLP-1 analogs, phentermine and topiramate, and bupropione and naltrexone combinations, they are known to act centrally at the central nervous system level to suppress appetite.[10,23] Therefore, a combination with a SGLT-2 inhibitor that may increase appetite would be really intriguing in terms of the weight-lowering efficacy.

Combinations of SGLT-2 inhibitors with other drugs for the treatment of T2D, such as dipeptidyl-peptidase inhibitors and insulin secretagogues, have been studied much better than the weight-lowering combinations.[92] In particular, there is growing evidence in favor of the combination of SGLT-2 inhibitors with GLP-1 analogs in T2D, if the cost is not a barrier.[93] In addition, the combination of SGLT-2 inhibitors with insulin has been suggested to lower HbA_{1c} levels and body weight gain caused by insulin treatment. However, an adjustment of the insulin dose to avoid hypoglycemia and the advent of EDKA should be borne in mind by the attending physicians.[94]

Conclusions SGLT-2 inhibitors, the class of antidiabetic agents named "the new kids on the block" in 2015 by Cefalu and Riddle,[20] seem to possess pleiotropic properties ranging from glycosuria to weight loss, cardioprotection and renoprotection.[10,20,23,95] Apart from their glucose-lowering effects, SGLT-2 inhibitors exhibit renoprotective properties, as they significantly improve the intraglomerular pressure, thereby ameliorating eGFR, while also reducing albuminuria.[10,23] In addition, they confer cardioprotection, especially in terms of improving HF, as documented by the decrease in the number of hospitalizations due to HF.[23] Furthermore, they seem to ameliorate NAFLD indices and promote weight loss, particularly in conjunction with the use of GLP-1 analogs.[96,97] Their utilization in obesity and obesity-related disorders seems beneficial, as they are also safe with rare severe adverse effects.[98] While the role of SGLT-2 inhibitors in the treatment of T2D and lately cardiac failure and chronic renal disease of nondiabetic etiology is already firmly established, their utility in the therapy of obesity, NAFLD, and other indications, alone or in combination with other agents will continue to be researched in the forthcoming years. Since the multifaceted mode of action and the potential benefits associated with the use of these agents continue to be elucidated, broadening of their clinical indications outside of the strict frame of diabetes will not come as a surprise.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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REFERENCES

1 Dalamaga M, Karampela I, Mantzoros CS. Commentary: phosphodiesterase 4 inhibitors as potential adjunct treatment targeting the cytokine storm in COVID-19. Metabolism. 2020; 109: 154282.

2 Hroussalas G, Kassi E, Dalamaga M, et al. Leptin, soluble leptin receptor, adiponectin and resistin in relation to OGTT in overweight/obese postmenopausal women. Maturitas. 2008; 59: 339-349.

3 Karampela I, Chrysanthopoulou E, Christodoulatos GS, Dalamaga M. Is there an obesity paradox in critical illness? Epidemiologic and metabolic considerations. Curr Obes Rep. 2020; 9: 231-244.

4 Marouga A, Dalamaga M, Kastania AN, et al. Correlates of serum resistin in elderly, non-diabetic patients with chronic kidney disease. Clin Lab. 2013; 59: 1121-1128.

5 Marouga A, Dalamaga M, Kastania AN, et al. Circulating resistin is a significant predictor of mortality independently from cardiovascular comorbidities in elderly, non-diabetic subjects with chronic kidney disease. Biomarkers. 2016; 21: 73-79.

6 World Health Organization. Obesity. https://www.who.int/health-topics/obesity#tab=tab_1. Accessed August 8, 2022.

7 World Health Organization. Global Report on Diabetes. April 21, 2016. https://www.who.int/publications/i/item/9789241565257. Accessed August 8, 2022.

8 Koziel P, Jankowski P, Mirek-Bryniarska E, et al. Obesity in patients with established coronary artery disease over a 20-year period (1997-2017). Pol Arch Intern Med. 2021; 131: 26-32.

9 Rajca A, Wojciechowska A, Smigielski W, et al. Increase in the prevalence of metabolic syndrome in Poland: comparison of the results of the WOBASZ (2003-2005) and WOBASZ II (2013-2014) studies. Pol Arch Intern Med. 2021; 131: 520-526.

10 Pereira MJ, Eriksson JW. Emerging role of SGLT-2 Inhibitors for the treatment of obesity. Drugs. 2019; 79: 219-230.

11 Fogarasi A, Gonzalez K, Dalamaga M, Magkos F. The impact of the rate of weight loss on body composition and metabolism. Curr Obes Rep. 2022; 11: 33-44.

12 Argyrakopoulou G, Konstantinidou SK, Dalamaga M, Kokkinos A. Nutritional deficiencies before and after bariatric surgery: prevention and treatment. Curr Nutr Rep. 2022; 11: 95-101.

13 Liu J, Tsilingiris D, Dalamaga M. The non-linear relationship between muscle mass and BMI calls into question the use of BMI as a major criterion for eligibility for bariatric surgery. Metabol Open. 2022; 13: 100164.

14 Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. Kidney Int Rep. 2022; 7: 1463-1476.

15 Zheng H, Liu M, Li S, et al. Sodium-glucose co-transporter-2 inhibitors in non-diabetic adults with overweight or obesity: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2021; 12: 706914.

16 Vick H, Diedrich DF, Baumann K. Reevaluation of renal tubular glucose transport inhibition by phlorizin analogs. Am J Physiol. 1973; 224: 552-557.

17 Rossetti L, Smith D, Shulman GI, et al. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987; 79: 1510-1515.

18 Valdes-Socin H, Scheen AJ, Jouret F, et al. From the discovery of phlorizin (a Belgian story) to SGLT2 inhibitors [in French]. Rev Med Liege. 2022; 77: 175-180.

19 Powell DR, Zambrowicz B, Morrow L, et al. Sotagliflozin decreases postprandial glucose and insulin concentrations by delaying intestinal glucose absorption. J Clin Endocrinol Metab. 2020; 105: e1235-e1249.

20 Cefalu WT, Riddle MC. SGLT2 inhibitors: the latest "new kids on the block"! Diabetes Care. 2015; 38: 352-354.

21 Dalamaga M, Christodoulatos GS, Karampela I, et al. Understanding the co-epidemic of obesity and COVID-19: current evidence, comparison with previous epidemics, mechanisms, and preventive and therapeutic perspectives. Curr Obes Rep. 2021; 10: 214-243.

22 Tentolouris A, Vlachakis P, Tzeravini E, et al. SGLT2 inhibitors: a review of their antidiabetic and cardioprotective effects. Int J Environ Res Public Health. 2019; 16: 2965.

23 Braunwald E. Gliflozins in the management of cardiovascular disease. N Engl J Med. 2022; 386: 2024-2034.

24 Xu L, Ota T. Emerging roles of SGLT2 inhibitors in obesity and insulin resistance: focus on fat browning and macrophage polarization. Adipocyte. 2018; 7: 121-128.

25 Ferrannini G, Hach T, Crowe S, et al. Energy balance after sodium-glucose cotransporter 2 inhibition. Diabetes Care. 2015; 38: 1730-1735.

26 Polidori D, Iijima H, Goda M, et al. Intra- and inter-subject variability for increases in serum ketone bodies in patients with type 2 diabetes treated with the sodium glucose co-transporter 2 inhibitor canagliflozin. Diabetes Obes Metab. 2018; 20: 1321-1326.

27 Rajeev SP, Sprung VS, Roberts C, et al. Compensatory changes in energy balance during dapagliflozin treatment in type 2 diabetes mellitus: a randomised double-blind, placebo-controlled, cross-over trial (ENERGIZE)-study protocol. BMJ Open. 2017; 7: e013539.

28 Dalamaga M, Papadavid E, Basios G, et al. Ovarian SAHA syndrome is associated with a more insulin-resistant profile and represents an independent risk factor for glucose abnormalities in women with polycystic ovary syndrome: a prospective controlled study. J Am Acad Dermatol. 2013; 69: 922-930.

29 Kassi E, Dalamaga M, Hroussalas G, et al. Adipocyte factors, high-sensitive C-reactive protein levels and lipoxidative stress products in overweight postmenopausal women with normal and impaired OGTT. Maturitas. 2010; 67: 72-77.

30 Koliaki C, Liatis S, Dalamaga M, Kokkinos A. The implication of gut hormones in the regulation of energy homeostasis and their role in the pathophysiology of obesity. Curr Obes Rep. 2020; 9: 255-271.

31 Sotiropoulos GP, Dalamaga M, Antonakos G, et al. Chemerin as a biomarker at the intersection of inflammation, chemotaxis, coagulation, fibrinolysis and metabolism in resectable non-small cell lung cancer. Lung Cancer. 2018; 125: 291-299.

32 Karampela I, Christodoulatos GS, Kandri E, et al. Circulating eNampt and resistin as a proinflammatory duet predicting independently mortality in critically ill patients with sepsis: a prospective observational study. Cytokine. 2019; 119: 62-70.

33 Dalamaga M, Liu J. Targeting gasdermin D and neutrophil mobilization for cardioprotection. Metabol Open. 2021; 12: 100152.

34 Dalamaga M, Liu J. A chromatin remodeling checkpoint of diet-induced macrophage activation in adipose tissue. Meatbol Open. 2022; 15: 100204.

35 LaMarche NM, Lynch L. Adipose dendritic cells come out of hiding. Cell Metab. 2018; 27: 485-486.

36 Macdougall CE, Wood EG, Loschko J, et al. Visceral adipose tissue immune homeostasis is regulated by the crosstalk between adipocytes and dendritic cell subsets. Cell Metab. 2018; 27: 588-601.e4.

37 Stratigou T, Muscogiuri G, Kotopouli M, et al. Lower circulating omentin-1 is independently linked to subclinical hypothyroidism reflecting cardiometabolic risk: an observational case-control and interventional, longitudinal study. Panminerva Med. 2022; Jun 17. [Epub ahead of print]

38 Tsilingiris D, Dalamaga M, Liu J. SARS-CoV-2 adipose tissue infection and hyperglycemia: a further step towards the understanding of severe COVID-19. Metabol Open. 2022; 13: 100163.

39 Tsigalou C, Vallianou N, Dalamaga M. Autoantibody production in obesity: is there evidence for a link between obesity and autoimmunity? Curr Obes Rep. 2020; 9: 245-254.

40 Arany Z. Taking a BAT to the chains of diabetes. N Engl J Med. 2019; 381: 2270-2272.

41 Kim SH, Plutzky J. Brown fat and browning for the treatment of obesity and related metabolic disorders. Diabetes Metab J. 2016; 40: 12-21.

42 Cheng L, Wang J, Dai H, et al. Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. Adipocyte. 2021; 10: 48-65.

43 van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009; 360: 1500-1508.

44 Hui X, Gu P, Zhang J, et al. Adiponectin enhances cold-induced browning of subcutaneous adipose tissue via promoting M2 macrophage proliferation. Cell Metab. 2015; 22: 279-290.

45 Inagaki T, Dutchak P, Zhao G, et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab. 2007; 5: 415-425.

46 Liu J, Dalamaga M. Emerging roles for stress kinase p38 and stress hormone fibroblast growth factor 21 in NAFLD development. Metabol Open. 2021; 12: 100153.

47 Reitman ML. FGF21: a missing link in the biology of fasting. Cell Metab. 2007; 5: 405-407.

48 Wu P, Wen W, Li J, et al. Systematic review and meta-analysis of randomized controlled trials on the effect of SGLT2 inhibitor on blood leptin and adiponectin level in patients with type 2 diabetes. Horm Metab Res. 2019; 51: 487-494.

49 Vallianou NG, Geladari E, Kazazis CE. SGLT-2 inhibitors: their pleiotropic properties. Diabetes Metab Syndr. 2017; 11: 311-315.

50 Vallianou NG, Stratigou T, Geladari E, et al. Diabetes type 1: can it be treated as an autoimmune disorder? Rev Endocr Metab Disord. 2021; 22: 859-876.

51 Karamanakos G, Kokkinos A, Dalamaga M, Liatis S. Highlighting the role of obesity and insulin resistance in type 1 diabetes and its associated cardiometabolic complications. Curr Obes Rep. 2022; 11: 180-202.

52 Brosius FC, Vandvik PO. Cardioprotection with yet another SGLT2 inhibitor - an embarrassment of riches. N Engl J Med. 2021; 384: 179-181.

53 Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med. 2017; 377: 2337-2348.

54 Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity (Silver Spring). 2014; 22: 1042-1049.

55 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373: 2117-2128.

56 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377: 644-657.

57 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019; 380: 347-357.

58 Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385: 1451-1461.

59 Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383: 1413-1424.

60 McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381: 1995-2008.

61 Masson W, Lavalle-Cobo A, Nogueira JP. Effect of SGLT2-inhibitors on epicardial adipose tissue: a meta-analysis. Cells. 2021; 10: 2150.

62 Neeland IJ, McGuire DK, Chilton R, et al. Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus. Diab Vasc Dis Res. 2016; 13: 119-126.

63 Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens. 2014; 8: 330-339.

64 Verma A, Patel AB, Waikar SS. SGLT2 inhibitor: not a traditional diuretic for heart failure. Cell Metab. 2020; 32: 13-14.

65 Batzias K, Antonopoulos AS, Oikonomou E, et al. Effects of newer antidiabetic drugs on endothelial function and arterial stiffness: a systematic review and meta-analysis. J Diabetes Res. 2018; 2018: 1232583.

66 Jardine MJ, Zhou Z, Mahaffey KW, et al. Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: a secondary analysis of the CREDENCE randomized trial. J Am Soc Nephrol. 2020; 31: 1128-1139.

67 Jardine MJ, Mahaffey KW, Neal B, et al. The canagliflozin and renal endpoints in diabetes with established nephropathy clinical evaluation (CREDENCE) study rationale, design, and baseline characteristics. Am J Nephrol. 2017; 46: 462-472.

68 Schernthaner G, Groop PH, Kalra PA, et al. Sodium-glucose linked transporter-2 inhibitor renal outcome modification in type 2 diabetes: evidence from studies in patients with high or low renal risk. Diabetes Obes Metab. 2020; 22: 1024-1034.

69 Heerspink HJL, Jongs N, Chertow GM, et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021; 9: 743-754.

70 Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003; 63: 793-808.

71 Schork A, Saynisch J, Vosseler 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.

72 Lei Y, Devarapu SK, Motrapu M, et al. Interleukin-1beta inhibition for chronic kidney disease in obese mice with type 2 diabetes. Front Immunol. 2019; 10: 1223.

73 Vallianou N, Christodoulatos GS, Karampela I, et al. Understanding the role of the gut microbiome and microbial metabolites in non-alcoholic

fatty liver disease: current evidence and perspectives. Biomolecules. 2021; 12: 56.

74 Younossi ZM. Non-alcoholic fatty liver disease – a global public health perspective. J Hepatol. 2019; 70: 531-544.

75 Divella R, Mazzocca A, Daniele A, et al. Obesity, nonalcoholic fatty liver disease and adipocytokines network in promotion of cancer. Int J Biol Sci. 2019; 15: 610-616.

76 Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. N Engl J Med. 2017; 377: 2063-2072.

77 Fotis D, Liu J, Dalamaga M. Could gut mycobiome play a role in NAFLD pathogenesis? Insights and therapeutic perspectives. Metabol Open. 2022; 14: 100178.

78 Al KF, Bisanz JE, Gloor GB, et al. Evaluation of sampling and storage procedures on preserving the community structure of stool microbiota: a simple at-home toilet-paper collection method. J Microbiol Methods. 2018; 144: 117-121.

79 Dalamaga M, Liu J. DRAK2-SRSF6-regulated RNA alternative splicing is a promising therapeutic target in NAFLD/NASH. Metabol Open. 2022; 13: 100157.

80 Mantovani A, Petracca G, Csermely A, et al. Sodium-glucose cotransporter-2 inhibitors for treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Metabolites. 2020; 11: 22.

81 Marinkovic-Radosevic J, Cigrovski Berkovic M, Kruezi E, et al. Exploring new treatment options for polycystic ovary syndrome: review of a novel antidiabetic agent SGLT2 inhibitor. World J Diabetes. 2021; 12: 932-938.

82 Javed Z, Papageorgiou M, Deshmukh H, et al. Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: a randomized controlled study. Clin Endocrinol (Oxf). 2019; 90: 805-813.

83 Palmer BF, Clegg DJ, Taylor SI, Weir MR. Diabetic ketoacidosis, sodium glucose transporter-2 inhibitors and the kidney. J Diabetes Complications. 2016; 30: 1162-1166.

84 Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab. 2015; 100: 2849-2852.

85 Halimi S, Verges B. Adverse effects and safety of SGLT-2 inhibitors. Diabetes Metab. 2014; 40: S28-S34.

86 Meraz-Munoz AY, Weinstein J, Wald R. eGFR decline after SGLT2 inhibitor initiation: the tortoise and the hare reimagined. Kidney360. 2021; 2: 1042-1047.

87 Chertow GM, Vart P, Jongs N, et al. Effects of dapagliflozin in stage 4 chronic kidney disease. J Am Soc Nephrol. 2021; 32: 2352-2361.

88 Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380: 2295-2306.

89 Cowan A, Jeyakumar N, Kang Y, et al. Fracture risk of sodium-glucose cotransporter-2 inhibitors in chronic kidney disease. Clin J Am Soc Nephrol. 2022; 17: 835-842.

90 American Diabetes Association Professional Practice C. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. Diabetes Care. 2022; 45: S17-S38.

91 Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895-e1032.

92 Kadowaki T, Yamamoto F, Taneda Y, et al. Effects of anti-diabetes medications on cardiovascular and kidney outcomes in Asian patients with type 2 diabetes: a rapid evidence assessment and narrative synthesis. Expert Opin Drug Saf. 2021; 20: 707-720.

93 Goldenberg RM, Ahooja V, Clemens KK, et al. Practical considerations and rationale for glucagon-like peptide-1 receptor agonist plus sodium-dependent glucose cotransporter-2 inhibitor combination therapy in type 2 diabetes. Can J Diabetes. 2021; 45: 291-302.

94 Yang Y, Zhao C, Ye Y, et al. Prospect of sodium-glucose co-transporter 2 inhibitors combined with insulin for the treatment of type 2 diabetes. Front Endocrinol (Lausanne). 2020; 11: 190.

95 Patoulias D, Papadopoulos C, Doumas M. Sodium-glucose cotransporter 2 inhibitors and heart failure decompensation: considerations on body composition and skeletal mass. Pol Arch Intern Med. 2021; 131: 16168.

96 Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021; 398: 262-276.

97 Brown E, Wilding JPH, Barber TM, et al. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: mechanistic possibilities. Obes Rev. 2019; 20: 816-828.

98 Tuttle KR, Brosius FC 3rd, Cavender MA, et al. SGLT2 Inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a scientific workshop sponsored by the National Kidney Foundation. Diabetes. 2021; 70: 1-16.