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Use of SGLT2 inhibitors in cardiovascular diseases: why, when and how? A narrative literature review

Lu Henri[a], Meyer Philippe[b], Hullin Roger[a]

[a] Department of Cardiology, Lausanne University Hospital and University of Lausanne, Switzerland
[b] Cardiology service, Department of Medicine, Geneva University Hospital and University of Geneva, Switzerland

Summary

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of drugs that reduce blood glucose levels by increasing urinary glucose excretion. On top of the glucose-lowering effect, they offer cardiovascular and renal benefits, the mechanisms of which are probably pleiotropic and include blood pressure reduction, volume depletion, weight loss and several metabolic effects (such as lipolysis and synthesis of ketone bodies). SGLT2 inhibitors are currently indicated in Europe and the USA, as first- or second-line treatments of type 2 diabetes mellitus (T2DM) in patients with established cardiovascular disease, high/very high cardiovascular risk, renal disease or heart failure. The use of dapagliflozin has recently been extended to patients with heart failure without T2DM, as new emerging data show benefits in this population. Despite an overall favourable safety profile, attention has to be paid to the increased risk of euglycaemic diabetic ketoacidosis and genital mycotic infections, as well as lower limb amputations and fractures, which have been inconsistently associated with SGLT2 inhibition. For the moment, cost related data for the Swiss setting is lacking but corresponding analyses from abroad suggest cost-effectiveness. Despite their numerous favourable cardiorenal implications, many physicians remain hesitant to use SGLT2 inhibitors. In this article, we present an up-to-date narrative literature review of the physiological mechanisms of action, current indications, therapeutic utility and side effects of SGLT2 inhibitors.

Keywords: *sodium-glucose cotransporter 2 inhibitor, type 2 diabetes mellitus, cardiovascular disease, renal disease*

Correspondence:
Dr Henri Lu, MD, Department of Cardiology, Lausanne University Hospital, Rue du Bugnon 46, CH-1011 Lausanne, henri.lu[at]chuv.ch

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are primarily a new class of glucose-lowering drugs. Today, dapagliflozin, canagliflozin, empagliflozin and ertugliflozin have all been approved for the treatment of type 2 diabetes mellitus (T2DM) by the European Medicines Agency (EMA), the US Food and Drugs Administration (FDA), and Swissmedic for combination therapy, mostly with metformin, or monotherapy in the case of metformin intolerance. This pharmacological class has also been shown to consistently improve cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM) with concomitant cardiovascular or chronic kidney disease, the reason why SGLT2 inhibition is now also approved for the treatment of these patients [1–4]. More recently, dapagliflozin has also been shown to reduce cardiovascular endpoints in patients with heart failure with reduced left ventricular ejection fraction (HFrEF) independently of the presence of T2DM [5]. As a consequence, dapagliflozin has been very recently approved by Swissmedic and the FDA for treatment of HFrEF [6].

Altogether, the large body of evidence from cardiovascular outcome trials in patients with T2DM, including overall more than 43,000 study participants, indicates broad application of these pharmacological agents in T2DM, which affects 6.9% among males and 4.4% among females of the Swiss population [7]. Furthermore, evidence from 4774 study participants with stable chronic HFrEF suggests that SGLT2 inhibition should be applied in every patient with HFrEF, and thus in almost 2% of the Swiss population [8].

However, SGLT2 inhibitors are only infrequently prescribed; the reasons may be a lack of familiarity, and knowledge of the indication, prescription modality and side effects [9].

In this article, we therefore present an up-to-date summary of current knowledge on SGLT2 inhibition, reviewing physiological mechanisms, evidence in literature, current indications, practical considerations for initiating the treatment and side effects.

Physiological mechanisms

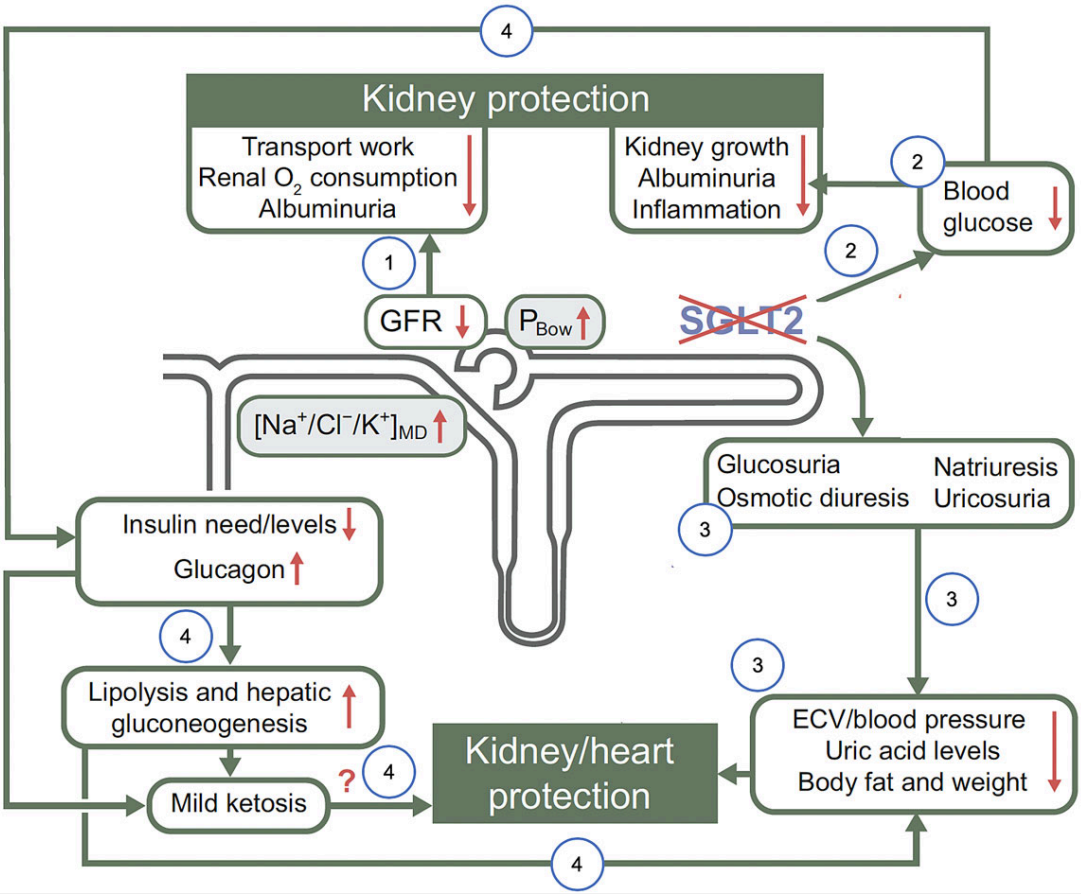
The SGLT2 is a sodium-dependent glucose transport protein, located in the proximal part of the proximal tubule of the nephron and involved in ~90% of glucose reabsorption from the primary urine back into the systemic circulation [10]. The remaining glucose is mostly reabsorbed in the distal part of the proximal tubule of the nephron, by the SGLT1 transporter [10].

Diabetes is associated with glomerular hyperfiltration and upregulation of SGLT2 expression, which results not only in increased reabsorption of urine glucose, but also sodium and water retention because SGLT2 couples glucose reabsorption with sodium co-transport [10, 11]. This decreases the urine volume and activates the tubuloglomerular feedback mechanism at the level of the macula densa resulting in glomerular hyperfiltration. Inhibition of the SGLT2 therefore not only improves glycaemic control in all stages of T2DM simply by inducing glycosuria but also increases natriuresis. Primary urine flow subsequently increases, resulting in deactivation of the tubuloglomerular feedback mechanism mediated by vasoconstriction of the nephron afferent arteriole. As a consequence, glomerular hyperfiltration and hydrostatic pressure in the Bowman's space decrease. The latter is a hallmark of kidney dysfunction in diabetes and one of the main causes of diabetes-associated albuminuria [11]. These beneficial changes not only restore the disturbed glomerulotubular balance in diabetes but, overall, improve renal function in the long-term [4] (fig. 1).

Glucose-lowering effect

SGLT2 inhibition furthermore results in significant improvement of glycaemic control [12] and significantly reduced glycated haemoglobin (HbA1c) [13]. In fact, an average reduction in HbA1c of 0.5 to 1% was consistently observed among all patients [14] and greater reductions have been described in patients with a baseline HbA1c of >8% [15]. This may suggest an increased risk of hypoglycaemia, however, the proximal tubule retains its glucose reabsorption capacity via the action of the SGLT1 when the filtered glucose load falls below ~80 g/day [11]. This explains why major hypoglycaemic events were rare and not more frequent in non-diabetic patients in the DAPA-HF study (4/2368 vs 4/2368 study participants) and is in line with the observation that clinically relevant hypoglycaemic events in the T2DM cardiovascular outcome tri-

Figure 1: The pleiotropic effects of sodium-glucose cotransporter 2 (SGLT2) inhibition. SGLT2 inhibition may provide its cardioprotective and renal protective effects via several pleiotropic mechanisms: (1) SGLT2 inhibition attenuates primary proximal tubular hyperreabsorption in the kidney in diabetes, increasing/restoring the tubuloglomerular feedback signal at the macula densa ($[Na^+/Cl^-/K^+]MD$) and hydrostatic pressure in Bowman's space (PBow). This reduces glomerular hyperfiltration, beneficially affecting albumin filtration and tubular transport work and, thus, renal oxygen consumption; (2) by lowering blood glucose levels, SGLT2 inhibitors can reduce kidney growth, albuminuria and inflammation; (3) SGLT2 inhibitors have a modest osmotic diuretic, natriuretic and uricosuric effect, which can reduce extracellular volume (ECV), blood pressure, serum uric acid levels and body weight; (4) SGLT2 inhibition reduces insulin levels and the need for therapeutic and/or endogenous insulin, and increases glucagon levels. As a consequence, lipolysis and hepatic gluconeogenesis are elevated. These metabolic adaptations reduce fat tissue/body weight and hypoglycaemia risk, and result in mild ketosis, potentially having beneficial effects on both the renal and cardiovascular systems. White text boxes indicate affected variables; grey text boxes indicate processes that link SGLT2 inhibition to the reduction in glomerular filtration rate (GFR). Green arrows demonstrate consequences; red arrows indicate changes in associated variables (increase/decrease). Reprinted by permission from Springer, Diabetologia, [Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017;60:215-25], copyright 2016.



als were most often associated with insulin or sulfonylurea treatment [5, 12].

Blood pressure-lowering effect

SGLT2 inhibition has been associated with beneficial vascular effects based on arterial vasodilation and improved endothelial function, which, combined with increased natriuresis and osmotic diuresis, can explain lower systemic blood pressure) and reduction of afterload [16]. These effects have been described with each of the four previously mentioned SGLT2 inhibitors regardless of T2DM patients' baseline blood pressure value [17]. The magnitude of blood pressure-lowering seems modest (about 3–4 mm Hg for systolic blood pressure and 1–2 mmHg for diastolic blood pressure [18]). However, study participants had either normal or well-controlled blood pressure when included into studies with SGLT2 inhibitors. In fact, greater blood pressure-lowering may be achieved in patients with higher blood pressure values [17]. Interestingly, SGLT2 inhibitors seem to restore a physiological blood pressure fall during sleep, changing the blood pressure circadian rhythm from a non-dipper profile (absence of nocturnal drop in blood pressure) to a dipper profile (nocturnal drop in blood pressure of 10–20%) [19]. This is all the more interesting since the non-dipper profile is associated with greater cardiovascular risk [19]. Moreover, the decrease in blood pressure and plasma volume is not associated with a rise in heart rate, suggesting an absence of secondary sympathetic activation. In accordance, recent experimental and clinical studies showed that SGLT2 inhibition reduces the sympathetic tone, probably via an indirect effect [17]. Indeed, it has been described that reduction in body weight results in a reduction of leptin stimulation and a decrease in the activation of the sympathetic nervous system [20]. It remains unclear to which extent these effects contribute to the favourable cardiovascular and renal outcomes of SGLT2 inhibitors.

Volume depletion

SGLT2 inhibitors increase natriuresis and osmotic diuresis resulting, in a decrease of the circulatory volume by almost 7% [21]. This is of particular interest in heart failure since preload and left ventricular filling pressures will decrease [22]. However, SGLT2 inhibition reduces volume overload not only by intravascular volume depletion but also by reduction of interstitial fluid volume, and the latter effect can even exceed the contraction of the intravascular volume mediated by loop diuretics or thiazide analogues [23]. This probably contributes to the modest elevation of haematocrit (2–4%) that has been observed on the biological level with all four SGLT2 inhibitors. Another explanation of the elevation of haematocrit could be an increase of erythropoietin production induced by SGLT2 inhibitors, the exact mechanism of which remains unclear [24]. All this may in fact explain the beneficial effects on cardiovascular endpoints, even in heart failure patients presenting with euvolaemia, who are at risk of developing acute kidney dysfunction due to prerenal hypovolaemia when treated with traditional diuretics [16]. Other differences between SGLT2 inhibitors and classic diuretics include electrolyte abnormalities, such as hypokalaemia and hypomagnesaemia, which are not commonly found with SGLT2 inhibitors [25], and metabolic abnormalities, such as hyperuricaemia, since SGLT2 inhibitors favour hypouricaemia via increased urinary uric acid excretion [10]. Although elevated uric acid levels have been associated with worse outcomes in patients with cardiovascular diseases [26], the clinical significance of hypouricaemia mediated by SGLT2 inhibition remains to be elucidated.

Weight loss

SGLT2 inhibitors usually induce a 2 to 3 kg decrease in body weight 24 to 52 weeks after treatment initiation [27]. This is in the early phase largely related to increased natriuretic and osmotic diuresis, as described above; however, the negative caloric balance from glycosuria also reduces visceral and subcutaneous fat [11]. The latter has been associated with reduction of systemic inflammation and decrease of cytokine production such as tumour necrosis factor-alpha (TNF-α) originating from visceral fat deposits [16]. Accordingly, SGLT2 inhibition has recently been shown to reduce fatty liver content and improve liver biological markers in patients with T2DM and non-alcoholic fatty liver disease [28].

Dapagliflozin was also shown to reduce epicardial fat mass and systemic TNF-α plasma levels after 6 months of treatment, which is of importance since TNF-α released from the epicardial adipose tissue has been shown to decrease myocardial function by paracrine and vasocrine interactions [29].

Metabolic effects of SGLT2 inhibition

SGLT2 inhibition has been related to favourable metabolic effects, especially in diabetic patients as compared with non-diabetic patients [30]. One important hypothesis to explain the favourable effects of SGLT2 inhibition in HFrEF and on cardiovascular endpoints is based on increased hepatic synthesis of ketone bodies (mainly of beta-hydroxybutyrate), enabling the failing cardiomyocyte to switch from less efficient beta-oxidation for energy production to more efficient glucose oxidation [31]. However, we have to acknowledge that ketone blood levels are variable; therefore, inter- and intra-subject variability accounting at least in part for the changes observed cannot be excluded [32]. Finally, some evidence suggests that SGLT2 inhibition may exert beneficial effects on the insulin pathway by reducing insulin resistance in target tissues (e.g., adipose tissue or the liver), and preserving insulin secretion capacity via protection of pancreatic beta-cells against glucose toxicity, thanks to mechanisms independent of urinary glucose secretion [33]. Further studies are needed to clarify these issues.

Other favourable effects of SGLT2 inhibition

In heart failure and in particular in diabetic cardiomyopathy, upregulation of sodium-hydrogen exchanger (NHE) 1 has been incriminated in the increase of cardiomyocyte cytoplasmic sodium and calcium levels [34]. SGLT2 inhibition, which blocks cardiomyocyte NHE 1 activation through an unknown mechanism, results in a reduction of cytoplasmic sodium levels and a subsequent mitochondrial calcium level increase [35]. The latter improves the metabolic efficiency of the mitochondrion and consequently cardiac contractility and global heart function [36]. However, SGLT2 inhibition likewise improves endothelial function [37], attenuates myocardial fibrosis [38] and in-

creases erythropoietin levels [39], which may also contribute to the cardiovascular benefit. Cardiovascular and renal benefits of SGLT2 inhibition are summarised in table 1.

Clinical evidence from cardiovascular and renal outcome trials

Type 2 diabetes mellitus

Evidence for the favourable effects of SGLT2 inhibition in patients with T2DM derives from three large, multicentre, randomised, double-blinded and placebo-controlled outcome trials investigating predefined cardiovascular endpoints (CVOTs), and a fourth one is underway.

The first one, the EMPA-REG OUTCOME trial, investigated in 7020 T2DM patients with overt cardiovascular disease the effect of empagliflozin on a primary combined endpoint of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke [1]. Empagliflozin was associated with a decrease of the primary outcome (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74–0.99; p = 0.04; number needed to treat [NNT] 62/3 years), mainly driven by a significant reduction in cardiovascular death (HR 0.62, 95% CI 0.49–0.77; p <0.001; NNT 45/3 years). Other results in favour of empagliflozin included a significant reduction of death from any cause (HR 0.68, 95% CI 0.57–0.82; p <0.001; NNT 38/3 years) and a significant reduction of hospitalisation for heart failure (HR 0.65, 95% CI 0.40–0.85; p = 0.002; NNT 72/3 years), with an early separation of Kaplan-Meier survival curves, suggesting an effect of the drug starting early-on, and illustrating the early effect of the pleiotropic actions described above. Moreover, although all patients had atherosclerotic cardiovascular disease, they had a broad risk spectrum for cardiovascular risk, with the beneficial effects of empagliflozin being consistent across the broad range of cardiovascular risk [40].

The second CVOT, the CANVAS Program study integrated data from two trials, the CANVAS (Canagliflozin Cardiovascular Assessment Study) study, which intended to show cardiovascular safety with the intention to get FDA approval, and the CANVAS-R (Canagliflozin Cardiovascular Assessment Study - Renal) study, which intended to study the effect of canagliflozin on albuminuria [2]. In total, these studies included 10142 T2DM patients suffering from either cardiovascular disease (65.6%) or high cardiovascular risk (34.4%). This study applied the same combined endpoint of major adverse cardiovascular events (MACE) as the EMPA-REG OUTCOME trial. The main result included a significant reduction of the primary outcome in favour of canagliflozin (three-point MACE, as defined above: HR 0.86, 95% CI 0.75-0.97; p = 0.02), but the components of the three-point MACE taken alone were not significant. Besides, in contrast to the EMPA-REG OUTCOME trial, all-cause mortality was not significantly reduced (HR 0.87, 95% CI 0.74–1.01). This may be partly explained by a different study population, as 65.6% of the participants of the CANVAS Program had a history of cardiovascular disease versus 100% in EMPAREG-OUTCOME. Still, canagliflozin use was associated with a significantly reduced rate of hospitalisation for heart failure (HR 0.67, 95% CI, 0.52–0.87; p <0.001).

The most recent CVOT, the DECLARE-TIMI-58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) investigated dapagliflozin versus placebo in 17,160 patients [3]. Unlike the two previous CVOTs, it included only 40.6% of patients with an established cardiovascular disease and 59.4% of T2DM patients presented only with cardiovascular risk factors. Dapagliflozin did not reduce the MACE rate, most likely because almost 60% of study participants were without overt cardiovascular disease. However, dapagliflozin significantly lowered the composite outcome of cardiovascular death or hospitalisation for heart failure (HR 0.83, 95% CI 0.730.95; p = 0.005; NNT, 111/4.2 years), and this effect was mainly driven by a substantially lower rate of hospitalisation for heart failure (HR 0.73, 95% CI 0.61–0.88; NNT 125/4.2 years), whereas there was no effect of cardiovascular mortality.

Table 1: Benefits, side effects and incidence rates of side effects associated with the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Benefits	Side effects	Incidence rates of side effects
Blood glucose-lowering effect	Genitourinary infections, mainly mycotic genital infections	Male – C: 34.9 p/1000 p-y – E: 5% Female – C: 68.8 p/1000 p-y – E: 10%
BP-lowering effect	Hypotension	C: 26 p/1000 p-y E: 5.1%
Weight loss	Acute kidney injury	C: 3 p/1000 p-y D: 1.5% E: 1.0%
Left ventricular filling pressures reductions, pre and afterload reductions	Risk of hypoglycaemia when associated with insulin or sulfonylurea	C: 50 p/1000 p-y E: 27.8%
Reduction of rates of MACE, CV mortality and hospitalisation for HF	Euglycaemic diabetic ketoacidosis	C: 0.6 p/1000 p-y D: 0.3% E: 0.1%
Improved renal outcomes – prevention of albuminuria – slowing of renal function decline	Amputations, mainly toe and metatarsal bones (only with canagliflozin) Low risk of fractures (only found with canagliflozin	C: 6.4 p/1000 p-y C:15.4 p/1000 p-y

CV = cardiovascular, HF = heart failure; MACE = major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; PAD = peripheral arterial disease; p/P-y = patients/1000 patient-years Incidence rates of side effects are based on the CANVAS-Program [2], DECLARE-TIMI 58 [3] and EMPAREG-OUTCOME [1] trials. They are expressed as number of patients for 1000 patient-years for canagliflozin (C), as percentages for dapagliflozin (D) and empagliflozin (E).

A fourth CVOT, the VERTIS CV (eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes, Clinicaltrials.gov identifier: NCT01986881) is underway to compare ertugliflozin versus placebo in T2DM subjects with established cardiovascular disease [41].

In a meta-analysis of the three CVOTs, SGLT2 inhibitors, as a drug class, significantly reduced the risk of MACE, mainly in patients with established cardiovascular diseases. In addition, this meta-analysis confirmed a reduction in the composite outcome of cardiovascular death or hospitalisation for heart failure, providing further evidence that empagliflozin, canagliflozin and dapagliflozin feature common pharmacological class effects in patients with heart failure that were initially unexpected [42].

Since all of these CVOTs showed that SGLT2 inhibitors may have beneficial effects in patients with T2DM and chronic kidney disease, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial was launched, comparing the effects of canagliflozin with placebo on a renal primary composite outcome (end-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes) [4]. All 4401 participants with T2DM and chronic kidney disease had an estimated glomerular filtration rate of 30 to <90 ml/min/1.73 m^2 (eGFR) and a ratio of albumin (mg) / creatinine (g) >300 to 5000, and were on maximum tolerated renin-angiotensin-aldosterone system antagonist treatment at baseline. In these study participants, canagliflozin treatment was associated with a significant reduction of the primary composite outcome (HR 0.70, 95% CI 0.59–0.82; p = 0.00001; NNT 22/2.5 years).

Evidence for beneficial effects in heart failure

Subanalyses of the EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI-58 trials suggested consistently that SGLT2 inhibitors may be particularly beneficial in patients with HFrEF [42–44]. This potential benefit was confirmed for dapagliflozin in the recently published pivotal DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) trial, which compared dapagliflozin with placebo in study participants on optimal standard heart failure therapy [5]. A particularity of this trial was that more than 50% of participants did not have T2DM among the 4744 patients with existing chronic HFrEF (left ventricular ejection fraction ≤40%) and an eGFR ≥30 ml/min/1.73 m^2. Non-diabetic participants were equally distributed between the two study groups and dapagliflozin was associated with a significant reduction of the primary outcome (a composite of heart failure-related hospitalisation, ambulatory urgent visit for heart failure decompensation, or cardiovascular death), with a HR of 0.74 (95% CI 0.65–0.85; p <0.001; NNT 21/18.4 months). Interestingly, findings in patients without T2DM were not different from those with T2DM, indicating that dapagliflozin has benefits in HFrEF management independent of the T2DM status.

The DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure, Clinicaltrials.gov identifier: NCT03619213) trial is underway to investigate the effects of dapagliflozin versus placebo in the management of heart failure with preserved ejection fraction (HFpEF), using the same primary endpoint as the DAPA-HF trial [41]. However, and despite high hopes that SGLT2-inhibition is beneficial in HFpEF, post-hoc preliminary analyses from the DECLARE-TIMI 58 study suggest that SGLT2 inhibition had no effect on cardiovascular mortality in HFpEF patients although still decreasing the incidence of hospitalisation for heart failure [45]. Nonetheless, a reduction of the incidence of hospitalisation for heart failure is relevant because of its long-term impact on survival, but this is clearly beyond the timeframe of a normal CVOT [46, 47]. Also, several other ongoing trials are exploring the effects of SGLT2 inhibitors in different settings (acute decompensated heart failure, chronic HFrEF and chronic HFpEF with and without T2DM), using various clinical and biological endpoints [41].

Side effects

Genitourinary infections

Genital mycotic infection (mainly vulvovaginitis in women and balanitis in men) is the most common side effect described for SGLT2 inhibitors [48]. In a large meta-analysis involving 36,689 patients, canagliflozin, dapagliflozin and empagliflozin were associated with a higher risk of genital mycotic infections than placebo, with odd ratios (ORs) ranging from 3.21 (95% CI 2.08–4.93) for dapagliflozin to 5.23 (95% CI 3.86–7.09) for canagliflozin [49]. Most infections are mild and easily treated with local antifungals [9]. For urinary tract infections, only dapagliflozin was associated with an increased risk (relative risk 1.21, 95% CI 1.02–1.43) but most were not severe [50]. The FDA has also reported cases of necrotising fasciitis of the perineum (Fournier's gangrene) [51]. These data were recently challenged by a large propensity score-matched study, including a total of 235,730 patients: compared with dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA), SGLT2 inhibitors were not associated with higher risks of urinary tract infection (HR 0.96, 95% CI 0.89–1.04 and HR 0.91, 95% CI 0.84–0.99, respectively) [52]. Nonetheless, patient information, education and self-monitoring are paramount.

Euglycaemic diabetic ketoacidosis

Euglycaemic diabetic ketoacidosis (EDKA), defined as a triad of normal glycaemia (<11 mmol/l), increased anion gap metabolic acidosis and ketonaemia or ketonuria, has been described in patients taking SGLT2 inhibitors [53]. Its incidence is low (~0.5 patients per 1000 patient-years) [54]. It is thought to be favoured by the ketone-based metabolism induced by SGLT2 inhibitors [10] and precipitation by additional factors, such as fasting, dehydration, discontinuation of insulin therapy, surgery, infections or excessive alcohol intake has been reported [55]. EDKA should be suspected in cases of nausea, vomiting or malaise, with serum ketones rapidly obtained and SGLT2 inhibitors discontinued. Because of the risk of severe EDKA, use in type 1 DM is contraindicated [56].

Acute kidney injury

There have been concerns regarding an increased risk of acute kidney injury associated with SGLT2 inhibitors, because of their natriuretic properties and effects on tubuloglomerular feedback [57]. In particular, the FDA issued

warnings regarding the use of canagliflozin and dapagliflozin in June 2016 following 101 cases of acute kidney injury [58].

A recent meta-analysis of the four CVOTs described above suggests the risk of acute kidney injury may actually be decreased (RR 0.74, 95% CI 0.66–0.85; p <0.0001) via renoprotective effects of SGLT2 inhibitors, the exact mechanisms of which are only partially understood [59]. We have to keep in mind that participants in randomised trials often receive close medical attention and follow-up, and it is unknown if this may have contributed to lowering the risk of acute kidney injury . However, regular follow-up for monitoring of kidney function, in particular in patients with concomitant diuretic treatment or diarrhoea, and adaptation of diuretic drug dose during heat waves should decrease the risk of acute kidney injury. Furthermore, discontinuation of SGLT2 inhibition is recommended in the case of planned surgical interventions.

Lower limb amputations

Only canagliflozin was shown to be associated with an increased risk of lower limb amputations, predominantly toe and metatarsal bones (6.3 vs 3.4 patients per 1000 patient-years in the active vs placebo groups of the CANVAS trial) [2, 60]. The risk was not dose-dependent and seemed to be increased in patients with previous lower limb amputations or with severe peripheral arterial disease [9]. Whether empagliflozin or dapagliflozin may be more suitable in at-risk patients remains to be shown. Regardless of the SGLT2 inhibitor used, patients should be regularly followed up for manifestations of peripheral artery disease.

Fractures

An increased risk of fractures has been reported with canagliflozin in the CANVAS trial (HR 1.26 95% CI 1.04–1.52) but was not found in the CANVAS-R trial [60]. Most fractures were nonvertebral. Empagliflozin and dapagliflozin have not been found to be associated with the same risk [48]. Possible mechanisms include an increased risk of falls due to volume depletion and orthostatic hypotension, and change in bone density [48].

Side effects of SGLT2 inhibitors are listed in table 1.

When and how to prescribe SGLT2 inhibitors?

The most recent available guidelines were published in 2020 by the American Diabetes Association (endorsed by the American College of Cardiology) and reflect the new evidence from CVOTs, with a special emphasis on early consideration of cardiovascular risk, heart failure or chronic kidney disease [61].

In patients with newly diagnosed T2DM and established cardiovascular disease, or at high / very high cardiovascular risk, the guidelines recommend using SGLT2 inhibitors (empagliflozin, canagliflozin or dapagliflozin) or GLP-1 RA as second-line treatments to reduce cardiovascular events, metformin remaining the first-line therapy [61].

In patients with T2DM and heart failure or chronic kidney disease, the SGLT2 inhibitors empagliflozin, canagliflozin and dapagliflozin are recommended as the preferred second-line treatments (after metformin) to lower the risk of heart failure hospitalisation or renal impairment [61].

In patients who do not belong to the these categories and whose HbA1c remains above target in spite of metformin therapy, SGLT2 inhibitors are on par with other drug classes (GLP-1 RA, DPP-4 inhibitors, thiazolidinediones) as second-line treatments [61].

Swiss guidelines from the Swiss Society of Endocrinology and Diabetology are mostly similar to the American ones, and recommend using SGLT2 inhibitors in combination with metformin in patients with T2DM and established atherosclerotic cardiovascular disease or at high cardiovascular risk [62].

The current indications of SGLT2 inhibitors in patients with T2DM and established cardiovascular disease, high cardiovascular risk, heart failure or chronic kidney disease, are summarised in figure 2.

European Society of Cardiology guidelines are slightly different in that SGLT2 inhibitors are recommended before metformin initiation in patients with T2DM and cardiovascular disease, high cardiovascular risk or heart failure [63].

In May 2020, dapagliflozin was further approved by the FDA and Swissmedic for all patients with heart failure presenting with a New York Heart Association (NYHA) II to IV functional class, with or without diabetes [6]. Exactly how and when to use dapagliflozin with regard to the already available heart failure treatments remains to be elucidated; however, consistently with the DAPA-HF trial, SGLT2 inhibition is certainly beneficial when HFrEF patients are already on stable optimal medical treatment.

Practical considerations about SGLT2 inhibitors initiation are presented in table 2.

Epidemiological and economic considerations

Diabetes is a major health issue worldwide, with Switzerland being no exception. The prevalence of diabetes in Switzerland in 2016 was estimated to be 6.9% among males and 4.4% among females [7]. Owing to population ageing and the rising prevalence of obesity, it is likely that the overall prevalence of diabetes will continue to grow in upcoming years. Furthermore, diabetes management constitutes an immense economic burden: total health care costs attributable to diabetes were estimated to be CHF 2.5 billion in 2011 [65]. More recent data for Switzerland are not available in literature, but between 2012 and 2017, the expenditure attributed to diabetes in neighbouring France was reported to increase by 2.3%/year [66], and it is likely that Switzerland followed a similar trend.

Heart failure is another growing global health concern, with an estimated prevalence of approximately 2–4% of the adult population in developed countries, rising to ≥10% among people aged 70 or more [8, 67]. By extrapolation of these data to Switzerland, the projected number of people living with HFrEF is somewhere between 85,000 and 170,000. Apart from mortality, heart failure is associated with significant comorbidities, impaired quality of life, considerable hospitalisation costs (heart failure is one of the leading causes of hospitalisation [68]) and use of medical resources [46]. In the United States in 2012, heart fail-

ure alone was estimated to be responsible for health expenditures of around USD 31 billion [69]. No data are available in the Swiss setting.

Because SGLT2 inhibitors are potent drugs in T2DM and heart failure, analysis of their cost-effectiveness in these particular settings is interesting. Unfortunately, few studies addressing this subject are available. A recent systematic review of literature found SGLT2 inhibitors to be cost-effective when compared with insulin, thiazolidinediones, sulfonylureas and DPP-4 inhibitors [70]. In Switzerland, if we take the example of dapagliflozin 10 mg, the price nationwide for 28 pills is CHF 69.50 (approximately EUR 66), with an estimated annual price of CHF 906.60 (EUR 862). Because of the significant improvements in terms of cardiovascular protection in patients with T2DM and reduction of hospitalisation risk in those with heart failure, this drug may be extremely cost-effective, with a significant reduction of health expenditures and use of medical resources.

Figure 2: Current indications for SGLT2 inhibitors in patients with type 2 diabetes mellitus and established cardiovascular disease, high cardiovascular risk, heart failure or chronic kidney disease.ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; CVOTs = cardiovascular outcomes trials; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; SGLT2i = sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Excerpt from the American Diabetes Association [Pharmacologic Approaches to Glycaemic Treatment: *Standards of Medical Care in Diabetes—2020*, American Diabetes Association, 2020]. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

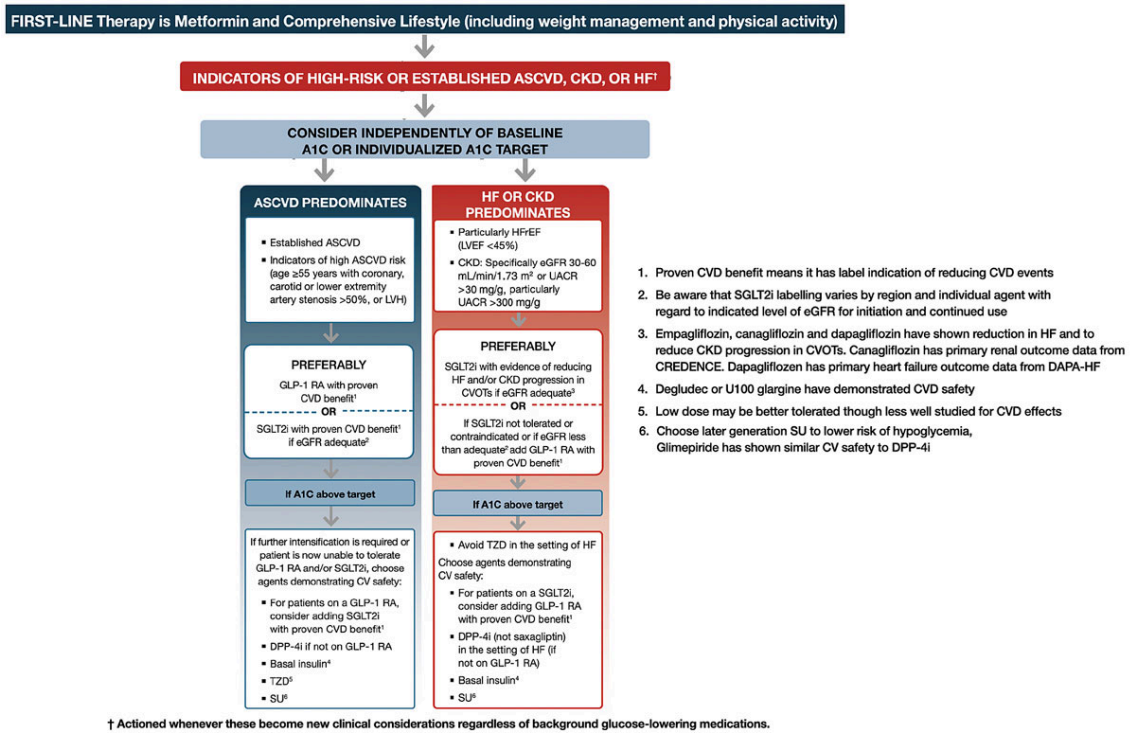


Table 2: Practical aspects of sodium-glucose cotransporter 2 (SGLT2) inhibitor prescription.

	Canagliflozin (Invokana®)	Dapagliflozin (Forxiga®)	Empagliflozin (Jardiance®)	Ertugliflozin (Steglatro®)
Swissmedic year of approval	January 2014	August 2014	December 2014	October 2018
Initial dose (maximum dose)	100 mg o.d. (300 mg o.d.)	5 mg o.d. (10 mg o.d.)	10 mg o.d. (25 mg o.d.)	5 mg o.d.
Administration	Before first meal	Morning without regard to food		
Price in Switzerland	CHF 66.95 (30 tablets)	CHF 69.50 (28 tablets)	CHF 74.20 (30 tablets)	CHF 65.95 (28 tablets)
Renal dosage adjustments	Caution is warranted when the eGFR is below 45 ml/min/1.73 m^2, while an eGFR below 30 m/min/1.73 m^2 or dialysis are absolute contraindications for SGLT2 inhibitors [41].			
Initiation requirements	Assessment of BP, volume status and renal function – Correction of hypovolaemia before SGLT2 inhibitors initiation [48] – Dose adjustment of BP-lowering drugs and diuretics, if necessary [48] In patients with insulin therapy or other glucose-lowering treatment at baseline (sulfonylurea or glinide), consider: – Lowering daily insulin dose by 20% – Reducing daily sulfonylurea or glinide dose by 50% (or discontinuing them if already on a minimal dose) [64].			
Patient information, counselling and self-monitoring	– Genital hygiene – Orthostatic hypotension – Close glycaemic monitoring in patients with other antidiabetic therapies – Regular foot examination – Symptoms of EDKA [12]			

BP = blood pressure; EDKA = euglycaemic diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; o.d. = once daily

Conclusions

SGLT2 inhibitors are a new class of drugs currently indicated for T2DM management. Although numerous studies have shown benefits on cardiovascular and renal outcomes in patients with T2DM and cardiovascular diseases, or at high / very high cardiovascular risk, the multiple mechanisms by which they protect cardiovascular and renal functions are still under investigation. Indications are rapidly changing: the FDA and Swissmedic have very recently granted the approval of dapagliflozin in patients with heart failure, including those without T2DM. As such, diabetologists, but also general practitioners, cardiologists and nephrologists are expected to become more involved in SGLT2 inhibitors initiation and management, in collaboration with other health care providers.

Potential competing interests

HL and RH have no conflict of interest regarding the publication of this article. PM has participated in meetings organised by Boehringer Ingelheim and Bayer, whose honoraria have been entirely paid to a private research foundation of the Cardiology Service of the University Hospitals of Geneva (GeCor foundation).

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(22):2117–28. doi: http://dx.doi.org/10.1056/NEJMoa1504720. PubMed.

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(7):644–57. doi: http://dx.doi.org/10.1056/NEJMoa1611925. PubMed.

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(4):347–57. doi: http://dx.doi.org/10.1056/NEJMoa1812389. PubMed.

4 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(24):2295–306. doi: http://dx.doi.org/10.1056/NEJMoa1811744. PubMed.

5 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(21):1995–2008. doi: http://dx.doi.org/10.1056/NEJMoa1911303. PubMed.

6 U.S. Food and Drug Administration. FDA approves new treatment for a type of heart failure [article online]. 2020. Available from https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure [Accessed 2020 May 13].

7 World Health Organization. Diabetes country profiles, Switzerland [article online]. 2016. Available from https://www.who.int/diabetes/country-profiles/che_en.pdf?ua=1 [Accessed 2020 May 11].

8 Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, et al. Treatment of chronic heart failure in Germany: a retrospective database study. Clin Res Cardiol. 2017;106(11):923–32. doi: http://dx.doi.org/10.1007/s00392-017-1138-6. PubMed.

9 Vardeny O, Vaduganathan M. Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists. JACC Heart Fail. 2019;7(2):169–72. doi: http://dx.doi.org/10.1016/j.jchf.2018.11.013. PubMed.

10 DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13(1):11–26. doi: http://dx.doi.org/10.1038/nrneph.2016.170. PubMed.

11 Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017;60(2):215–25. doi: http://dx.doi.org/10.1007/s00125-016-4157-3. PubMed.

12 Gomez-Peralta F, Abreu C, Lecube A, Bellido D, Soto A, Morales C, et al. Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes. Diabetes Ther. 2017;8(5):953–62. doi: http://dx.doi.org/10.1007/s13300-017-0277-0. PubMed.

13 Custodio JS, Jr, Duraes AR, Abreu M, Albuquerque Rocha N, Roever L. SGLT2 inhibition and heart failure-current concepts. Heart Fail Rev. 2018;23(3):409–18. doi: http://dx.doi.org/10.1007/s10741-018-9703-2. PubMed.

14 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(4):262–74. doi: http://dx.doi.org/10.7326/0003-4819-159-4-201308200-00007. PubMed.

15 Hardy E, Salsali A, Hruba V, Mansfield T, Rohwedder K, Wessman C, et al. Efficacy increases with increasing baseline HbA1c category with dapagliflozin therapy. Diabetes. 2012;61(Suppl.1):23.

16 Filippatos TD, Liontos A, Papakitsou I, Elisaf MS. SGLT2 inhibitors and cardioprotection: a matter of debate and multiple hypotheses. Postgrad Med. 2019;131(2):82–8. doi: http://dx.doi.org/10.1080/00325481.2019.1581971. PubMed.

17 Scheen AJ. Effect of SGLT2 Inhibitors on the Sympathetic Nervous System and Blood Pressure. Curr Cardiol Rep. 2019;21(8):70. doi: http://dx.doi.org/10.1007/s11886-019-1165-1. PubMed.

18 Pham SV, Chilton R. EMPA-REG OUTCOME: the cardiologist's point of view. Am J Med. 2017;130(6S):S57–62. doi: http://dx.doi.org/10.1016/j.amjmed.2017.04.006. PubMed.

19 Rahman A, Hitomi H, Nishiyama A. Cardioprotective effects of SGLT2 inhibitors are possibly associated with normalization of the circadian rhythm of blood pressure. Hypertens Res. 2017;40(6):535–40. doi: http://dx.doi.org/10.1038/hr.2016.193. PubMed.

20 Packer M. Leptin-Aldosterone-Neprilysin Axis: Identification of Its Distinctive Role in the Pathogenesis of the Three Phenotypes of Heart Failure in People With Obesity. Circulation. 2018;137(15):1614–31. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.117.032474. PubMed.

21 Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. J Cardiol. 2018;71(5):471–6. doi: http://dx.doi.org/10.1016/j.jjcc.2017.12.004. PubMed.

22 Bertero E, Prates Roma L, Ameri P, Maack C. Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. Cardiovasc Res. 2018;114(1):12–8. doi: http://dx.doi.org/10.1093/cvr/cvx149. PubMed.

23 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(9):853–62. doi: http://dx.doi.org/10.1111/dom.12127. PubMed.

24 Sano M, Goto S. Possible Mechanism of Hematocrit Elevation by Sodium Glucose Cotransporter 2 Inhibitors and Associated Beneficial Renal and Cardiovascular Effects. Circulation. 2019;139(17):1985–7. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.118.038881. PubMed.

25 Tsimihodimos V, Karanatsis N, Tzavela E, Elisaf M. Antidiabetic drugs and the kidney. Curr Pharm Des. 2017;23(41):6310–20. doi: http://dx.doi.org/10.2174/1381612823666170307103222. PubMed.

26 Ndrepepa G, Braun S, King L, Hadamitzky M, Haase HU, Birkmeier KA, et al. Association of uric acid with mortality in patients with stable coronary artery disease. Metabolism. 2012;61(12):1780–6. doi: http://dx.doi.org/10.1016/j.metabol.2012.05.014. PubMed.

27 Kaplan A, Abidi E, El-Yazbi A, Eid A, Booz GW, Zouein FA. Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects. Heart Fail Rev. 2018;23(3):419–37. doi: http://dx.doi.org/10.1007/s10741-017-9665-9. PubMed.

28 Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: A common comorbidity associated with severe complications. Diabetes Metab. 2019;45(3):213–23. doi: http://dx.doi.org/10.1016/j.diabet.2019.01.008. PubMed.

29 Sato T, Aizawa Y, Yuasa S, Kishi S, Fuse K, Fujita S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc Diabetol. 2018;17(1):6. doi: http://dx.doi.org/10.1186/s12933-017-0658-8. PubMed.

30 Al Jobori H, Daniele G, Adams J, Cersosimo E, Triplitt C, DeFronzo RA, et al. Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. Diabetes Obes Metab. 2017;19(6):809–13. doi: http://dx.doi.org/10.1111/dom.12881. PubMed.

31 Gormsen LC, Svart M, Thomsen HH, Søndergaard E, Vendelbo MH, Christensen N, et al. Ketone body infusion with 3-hydroxybutyrate reduces myocardial glucose uptake and increases blood flow in humans: a positron emission tomography study. J Am Heart Assoc. 2017;6(3):e005066. doi: http://dx.doi.org/10.1161/JAHA.116.005066. PubMed.

32 Polidori D, Iijima H, Goda M, Maruyama N, Inagaki N, Crawford PA. 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(5):1321–6. doi: http://dx.doi.org/10.1111/dom.13224. PubMed.
33 Kaneto H, Obata A, Kimura T, Shimoda M, Okauchi S, Shimo N, et al. Beneficial effects of sodium-glucose cotransporter 2 inhibitors for preservation of pancreatic β-cell function and reduction of insulin resistance. J Diabetes. 2017;9(3):219–25. doi: http://dx.doi.org/10.1111/1753-0407.12494. PubMed.
34 Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiol. 2017;2(9):1025–9. doi: http://dx.doi.org/10.1001/jamacardio.2017.2275. PubMed.
35 Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JWT, Koeman A, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na^+/H^+ exchanger, lowering of cytosolic Na^+ and vasodilation. Diabetologia. 2018;61(3):722–6. doi: http://dx.doi.org/10.1007/s00125-017-4509-7. PubMed.
36 Despa S, Islam MA, Weber CR, Pogwizd SM, Bers DM. Intracellular Na(+) concentration is elevated in heart failure but Na/K pump function is unchanged. Circulation. 2002;105(21):2543–8. doi: http://dx.doi.org/10.1161/01.CIR.0000016701.85760.97. PubMed.
37 Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol. 2017;16(1):138. doi: http://dx.doi.org/10.1186/s12933-017-0621-8. PubMed.
38 Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017;104:298–310. doi: http://dx.doi.org/10.1016/j.freeradbiomed.2017.01.035. PubMed.
39 Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 Inhibitors in Heart Failure: Current Management, Unmet Needs, and Therapeutic Prospects. J Am Heart Assoc. 2019;8(20):e013389. doi: http://dx.doi.org/10.1161/JAHA.119.013389. PubMed.
40 Fitchett D, Inzucchi SE, Cannon CP, McGuire DK, Scirica BM, Johansen OE, et al. Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. Circulation. 2019;139(11):1384–95. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.118.037778. PubMed.
41 Seferović PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, et al. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. Eur J Heart Fail. 2020;22(2):196–213. doi: http://dx.doi.org/10.1002/ejhf.1673. PubMed.
42 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(10166):31–9. doi: http://dx.doi.org/10.1016/S0140-6736(18)32590-X. PubMed.
43 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(5):458–68. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.118.034222. PubMed.
44 Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139(22):2528–36. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.119.040130. PubMed.
45 Verma S, McMurray JJV. The Serendipitous Story of SGLT2 Inhibitors in Heart Failure: New Insights From DECLARE-TIMI 58. Circulation. 2019;139(22):2537–41. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.119.040514. PubMed.
46 Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol. 2015;12(4):220–9. doi: http://dx.doi.org/10.1038/nrcardio.2015.14. PubMed.
47 Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol. 2017;70(20):2476–86. doi: http://dx.doi.org/10.1016/j.jacc.2017.08.074. PubMed.
48 Opingari E, Partridge ACR, Verma S, Bajaj HS. SGLT2 inhibitors: practical considerations and recommendations for cardiologists. Curr Opin Cardiol. 2018;33(6):676–82. doi: http://dx.doi.org/10.1097/HCO.0000000000000561. PubMed.
49 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(3):348–55. doi: http://dx.doi.org/10.1111/dom.12825. PubMed.
50 Donnan JR, Grandy CA, Chibrikov E, Marra CA, Aubrey-Bassler K, Johnston K, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. BMJ Open. 2019;9(1):e022577. doi: http://dx.doi.org/10.1136/bmjopen-2018-022577. PubMed.
51 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(11):764–9. doi: http://dx.doi.org/10.7326/M19-0085. PubMed.
52 Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. Ann Intern Med. 2019;171(4):248–56. doi: http://dx.doi.org/10.7326/M18-3136. PubMed.
53 Rawla P, Vellipuram AR, Bandaru SS, Pradeep Raj J. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. Endocrinol Diabetes Metab Case Rep. 2017;2017:17–0081. doi: http://dx.doi.org/10.1530/EDM-17-0081. PubMed.
54 Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes Care. 2015;38(9):1638–42. doi: http://dx.doi.org/10.2337/dc15-1380. PubMed.
55 Dizon S, Keely EJ, Malcolm J, Arnaout A. Insights into the recognition and management of SGLT2-inhibitor-associated ketoacidosis: it's not just euglycemic diabetic ketoacidosis. Can J Diabetes. 2017;41(5):499–503. doi: http://dx.doi.org/10.1016/j.jcjd.2017.05.004. PubMed.
56 Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. J Clin Endocrinol Metab. 2015;100(8):2849–52. doi: http://dx.doi.org/10.1210/jc.2015-1884. PubMed.
57 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(11):1479–85. doi: http://dx.doi.org/10.2337/dc17-1011. PubMed.
58 U.S. Food and Drug Administration. FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR) [article online]. 2016. Available from https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm. [Accessed 2020 July 2].
59 Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019;7(11):845–54. doi: http://dx.doi.org/10.1016/S2213-8587(19)30256-6. PubMed.
60 Arnott C, Li Q, Kang A, Neuen BL, Bompoint S, Lam CSP, et al. Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2020;9(3):e014908. doi: http://dx.doi.org/10.1161/JAHA.119.014908. PubMed.
61 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S98–110. doi: http://dx.doi.org/10.2337/dc20-S009. PubMed.
62 Schweizerische Gesellschaft für Endokrinologie und Diabetologie (SGED). [article online]. 2020. Available from https://www.sgedssed.ch/fileadmin/user_upload/6_Diabetologie/61_Empfehlungen_Facharzt/2020_Swiss_Recomm_Medis_EN_def.pdf [Accessed 2020 2 July].
63 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. Eur Heart J. 2020;41(2):255–323. doi: http://dx.doi.org/10.1093/eurheartj/ehz486. PubMed.
64 Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL, Jr, et al. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018;72(24):3200–23. doi: http://dx.doi.org/10.1016/j.jacc.2018.09.020. PubMed.
65 Huber CA, Schwenkglenks M, Rapold R, Reich O. Epidemiology and costs of diabetes mellitus in Switzerland: an analysis of health care claims data, 2006 and 2011. BMC Endocr Disord. 2014;14(1):44. doi: http://dx.doi.org/10.1186/1472-6823-14-44. PubMed.
66 Denis P, Aguadé A, Lesuffleur T, Pestel L, Nicolas M, Rachas A, et al. Economic burden of diabetes in France between 2012 and 2017 based on French national claim database. Eur J Public Health. 2019;29(Sup-

plement_4): ckz187.068. doi: http://dx.doi.org/10.1093/eurpub/ckz187.068.

67 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 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(27):2129–200. doi: http://dx.doi.org/10.1093/eurheartj/ehw128. PubMed.

68 Stewart S, Ekman I, Ekman T, Odén A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes. 2010;3(6):573–80. doi: http://dx.doi.org/10.1161/CIRCOUTCOMES.110.957571. PubMed.

69 Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al.; Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38–360. doi: http://dx.doi.org/10.1161/CIR.0000000000000350. PubMed.

70 Hong D, Si L, Jiang M, Shao H, Ming WK, Zhao Y, et al. Cost Effectiveness of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors, Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists, and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: A Systematic Review. Pharmacoeconomics. 2019;37(6):777–818. PubMed.