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REVIEW

The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder associated with high cardiovascular (CV) risk. Some of the therapeutic strategies are contraindicated in patients with concomitant heart disease. However, the newest antidiabetic medications, sodium-glucose cotransporter 2 (SGLT2) inhibitors, have shown to significantly reduce CV mortality and heart failure (HF) hospitalizations. The mechanism behind these surprising cardiac benefits remains unclear.

Areas covered: This article reviews the pharmacokinetic, pharmacodynamics, efficacy, and safety data for the different SGLT2 inhibitors. Specific attention is devoted to the postulated mechanisms of action for their benefit. The therapeutic efficacy and potential use in different indications outside T2DM such as HF, T1DM, and renal disease are also discussed.

Expert opinion: SGLT2 inhibitors have an excellent pharmacokinetic and pharmacodynamic profile. Importantly, SGLT2 inhibitors are a safe and efficacious treatment option for T2DM. Given their cardiac benefits (reduction in HF and death) and the low incidence of adverse events, SGLT2 inhibitors are being currently studied as a treatment for HF also in nondiabetic individuals. These agents seem to represent a shift in the treatment of HF patients regardless their glycemic profile.

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1. Introduction

The worldwide prevalence of diabetes mellitus (DM) has almost doubled from 4.7% to 8.5% between 1980 and 2014, with a total of 422 million of diabetic adults. By 2040, it is predicted that there will be 642 million people with DM. In 2012, a total of 1.7 million new cases were diagnosed among US adults, and the cost of DM was estimated at $245 billion (i.e. 1 in 5 healthcare dollars). Among patients above 65 years of age with DM, almost 70% died of some form of heart disease. Moreover, cardiac mortality is two to four times higher in adults with DM than adults without [1].

Type 2 diabetes (T2DM) accounts for 90–95% of all diabetes cases [1]. It represents a significant healthcare burden and increases the risk of acquiring serious macrovascular and microvascular complications. Such macrovascular conditions include myocardial infarction (MI), stroke, and peripheral artery disease. Additionally, T2DM leads to microvascular complications such us neuropathy, retinopathy, and nephropathy. The risk of complications increases with higher levels of glycated hemoglobin (HbA1c) [2]. The benefits of optimal glycemic control on the incidence of microvascular complications is well established [3], but its effects on macrovascular outcomes remains controversial. Nonetheless, some studies suggest that aggressive lowering of HbA1c levels (<6.0%) would rather increase otherwise the risks of hypoglycemia and complications [4,5].

T2DM is a complex metabolic and cardiovascular (CV) disorder involving different organs. Classically, it has been considered as insulin resistance (IR) in skeletal muscle and liver, combined with insulin secretion defects (due to pancreatic β-cell dysfunction). Recently six more pathophysiologic mechanisms have been added to this list of pathophysiological mechanisms thus, completing the so-called 'ominous octet' [6]. These mechanisms affect gastrointestinal tract (incretin deficiency/resistance and accelerated gastric emptying), pancreatic α-cells (increased glucagon secretion), adipocytes (accelerated lipolysis), kidneys (increased glucose reabsorption), and brain (appetite control, neurotransmitter dysregulation and IR).

Tight control of glycemia (HbA1c < 7%) may diminish diabetic complications. Other authors suggest more stringent control (HbA1c < 6.5%) for selected individuals, such as those without CV disease (primary prevention) or short duration of diabetes, if this can be achieved without significant hypoglycemia. On the other hand, more flexible or less intense glycemic goals (HbA1c < 8%) should be implemented in older patients and those with high burden of comorbidities, since hypoglycemic events may result in higher mortality in these patients [7,8]. Therefore, a careful and individualized approach is highly recommended

2. Overview of the market

The characteristics of most commonly used lowering-glucose medications, including mechanism of action and major outcomes, are listed in Table 1 [7–35].

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Article highlights

- Type 2 diabetes mellitus (T2DM) increases cardiovascular risk.
- Managing patients with already established heart disease and T2DM is challenging since some of the antidiabetic drugs are contraindicated in such patients.
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors, by blocking renal reabsorption of glucose, are safe and well-tolerated agents to treat diabetic patients.
- SGLT2 inhibitors have significantly shown to reduce mortality and HF hospitalizations in T2DM patients and therefore, they may represent an alternative in these individuals.
- These new drugs also slow down progression of kidney disease, which is a condition frequently associated with diabetes.
- The mechanism behind these surprising findings remains unclear (myocardial ketone utilization? sodium-hydrogen exchanger inhibition? lowering blood pressure and arterial stiffness? diuretic effect?).

This box summarizes key points contained in the article.

- **Biguanides**: Metformin is the worldwide accepted first-line therapy for T2DM. Metformin decrease hepatic glucose production mainly by inhibiting gluconeogenesis enhance peripheral insulin sensitivity in the skeletal muscle [7,29], with low risk for hypoglycemia and without causing weight gain [29]. Metformin improves diabetes-related endpoints and all-cause mortality [30]; specifically, it is safe for HF patients and does not worsen HF outcomes [31].
- **Sulfonylureas (SFUs)**: Sulfonylureas (first-generation drugs: chlorpropamide; second-generation: Glyburide/glibenclamide and glipizide; third-generation: glimepiride and gliclazide) were the first oral antidiabetic medications used. They increase insulin secretion by binding to the sulphonylurea receptor 1 (SUR1) on the pancreatic β-cell membrane, thus their effect is independent of plasma glucose concentrations, leading to increased risk of hypoglycemia. They also cause weight gain. SFUs are now considered second- or third-line drugs because they increased risk of all-cause mortality and CV death [32] and acute decompensated HF [33].
- **Meglitinides** (repaglinide, meglitinide, and nateglinide): They share mechanism of action with SFUs but with shorter duration of action due to weaker binding affinity and faster dissociation from SUR1, thus also causing some hypoglycemia and weight gain. They can be administered three times per day with meals and be omitted if a meal is skipped, which is a useful option for patients with irregular meal schedule. Meglitinides have failed to demonstrate a reduction in CV events [34] and also showed the highest incidence of HF hospitalization compared with SFUs and acarbose [35].
- **Alpha-Glucosidase inhibitors** (acarbose and miglitol): Their inhibitory action on the enzyme α-glucosidase slows the digestion of carbohydrates and delays glucose absorption, thus not causing hypoglycemia. A meta-analysis suggested that acarbose reduces MI and CV events [9], but no data regarding HF risk have been published.
- **Thiazolidinediones (TZDs)**: Rosiglitazone and pioglitazone are PPARy agonists that reduce insulin resistance in the skeletal muscle and adipose tissue. They also activate sodium channels in the distal nephron leading to their common side effect, water retention, thus precipitating HF episodes [7]. In fact, they doubled the risk of HF hospitalizations or HF deaths [10,11,19]. Rosiglitazone particularly, increased MI risk [12,13] which lead the FDA to issue a guidance for industry in December 2008, recommending that any clinical trial of antidiabetic should specifically include evaluation of CV safety.
- **Insulin**: Insulin is obviously first-line therapy for T1DM but is classically regarded as the last choice in the treatment of T2DM, when β-cell function is severely limited. It is also beneficial if oral antidiabetic medications are contraindicated and should be considered at first-line in patients presenting with HbA1c > 9% or in pregnancy [7]. A meta-analysis including 18,599 patients reported that insulin had no effects on all-cause mortality nor CV mortality versus hypoglycemic drugs [14], but hypoglycemia and weight gain were more frequent. There are no specific data about insulin and HF risk.
- **GLP-1 receptor antagonists (GLP-1RA)**: In healthy individuals, oral ingestion of glucose promotes a greater insulin response than parenteral infusion, a response known as incretin effect. GLP-1 and GIP, the incretin hormones, are released by gut cells in response to the presence of nutrients (especially carbohydrates and lipids), and are degraded by the plasmatic enzyme DPP-4. Incretins bind GLP-1 receptors and have three main effects: (1) stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, (2) slow gastric emptying, and (3) reduce appetite and food intake [7]. GLP-1 also exerts beneficial effects at cardiac level. GLP-1 infusion significantly improved left ventricular systolic function in animal models of HF [15] and in HF patients [16]. In addition, exenatide ameliorates myocardial ischemia-reperfusion injury hence reducing MI size in animal models [17] and patients [18]. The main limitation of the GLP-1RA is the subcutaneous instead of oral administration. Short-acting GLP-1RA (exenatide and lixisenatide) are more effective in lowering postprandial hyperglycemia, while long-acting GLP-1RA (albiglutide, liraglutide, semaglutide, and dulaglutide) improve basal hyperglycemia, which resembles the action of prandial and basal insulin preparations [7]. In placebo-controlled trials exenatide showed a dose-dependent hypoglycemic effect. The LEAD program [20] compared liraglutide with widely used classes of antidiabetic drugs in a series of randomized, double-blind, controlled studies in patients with T2DM and inadequately controlled glucose. These studies showed that the combination of liraglutide with other oral antidiabetic drugs significantly improved glycemic control and weight loss. Furthermore, once-weekly semaglutide as an add-on to oral antidiabetic drugs

Table 1. Characteristics of commonly used hypoglycemic drugs and its cardiovascular risk.

Medications	Mechanism of action	Special considerations	CV outcomes	Other outcomes
Biguanides (i.e. Metformin)	Multiple: • ↓ Hepatic glucose production by inhibiting gluconeogenesis • ↑ Peripheral insulin sensitivity in the skeletal muscle *It does not induce insulin secretion.	• Contraindicated in patients prone to develop metabolic acidosis (CKD* Liver failure; HF (NYHA class IV); Major surgery; Sepsis; Alcoholism; IV contrast iodine (for 24)	• They may improve survival rates in stable HF patients with T2DM	• Neutral hypoglycemic effects
Sulfonylureas (i.e. Chlorpropamide, Glibenclamide, Gliclazide)	Insulin secretagogues	• Contraindicated in HF patients • Its effect is independent of plasma glucose concentrations	• They may increase mortality rates (including CV death). Third-generation SUs may have a safer profile	• Risk of moderate to severe hypoglycemia
Meglitinides (i.e. Repaglinide)	Insulin secretagogues	• Contraindicated in HF patients	• Unclear CV risk (Repaglinide might improve CV outcomes)	• Risk of mild to moderate hypoglycemia.
α-Glucosidase inhibitors	GI glucose absorption delay	• No HF patients data	• Acarbose may reduce CV adverse events	• Neutral hypoglycemic effects
Thiazolidinediones (i.e. Rosiglitazone, Pioglitazone)	Multiple: • ↑ Glucose uptake by skeletal muscle • ↑ β-cell function • ↑ Insulin sensitivity in the adipose tissue/skeletal muscle/liver • ↑ Distal nephron sodium channels activation (thus water retention)	• Contraindicated in HF patients (NYHA III-IV) • Common side effect: water retention • Caution in PAD patients	• Rosiglitazone has been associated with increased risk of MI and HF hospitalizations	• No significant increase of hypoglycemia rates • Benefits on dyslipidemia and hypertension • Pioglitazone may be associated with bladder cancer
Insulin	• Promoting glucose disposal	• Alternative when oral antidiabetic drugs are contraindicated (i.e. HF)	• No increased risk of CV outcomes	• Caution with hypoglycemia in HF patients
DPP-4 inhibitors	• Glucose-dependent insulin secretion via incretin system	• Not contraindicated in HF	• Saxagliptin may worsen HF prognosis	• No significant increase of hypoglycemia
GLP-1 agonists	• Glucose-dependent insulin secretion via incretin system	• Not contraindicated in HF	• They improve CV outcomes (they decrease infarct size, total death and improve EF)	• No significant increase of hypoglycemia

*CKD: chronic kidney disease (with eGFR < 30 mL/min/1.73 m^2); CV: cardiovascular; DPP-4: *dipeptidyl peptidase-4*; EF: *ejection fraction*; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; GLP-1: *Glucagon-like peptide-1;* HF: heart failure; IV: intravenous; MI: myocardial infarction; NYHA: New York Heart Association; PAD: peripheral arterial disease; T2DM: type-2 diabetes

seems to be the most efficacious of the GLP-1 RA in terms of HbA1c and weight reduction [21]. Likewise, semaglutide is well tolerated and not associated with effects compared with other GLP-1 RA. All GLP-1RA have demonstrated to improve glycemic control and reduce diabetic complications, either in monotherapy or in combination [7]. But only two GLP-1RA have demonstrated CV benefits. Liraglutide once daily showed in the LEADER clinical trial a significant 13% reduction in the primary endpoint of three-point MACE; only CV mortality reached significance with a nonsignificant reductions in MI and stroke as compared with placebo [22]. Semaglutide, a once-a-week GLP-1RA, has also shown in the SUSTAIN-6 trial a reduction on the three-point major adverse CV events (MACE) [21]. The rest of GLP-1RA have not demonstrated CV benefits: neither exenatide in the EXSCEL trial [23] nor lixisenatide in the ELIXA trial [24]. A recent meta-analysis of all GLP-1 RA trials with CV outcomes concluded that GLP-1RA have a favorable risk-benefit balance overall [25].

- **Dipeptidyl peptidase-4 (DPP-4) inhibitors**: This class of drugs acts by preventing the degradation of the incretin hormones via inhibiting DPP-4 (the plasmatic enzyme degrading GLP-1). These agents have a low risk of hypoglycemia and are weight neutral [7,19]. The most commonly used DDP-4 inhibitors are sitagliptin, alogliptin, linagliptin, and saxagliptin. Recently reported trials (SAVOR [26], EXAMINE [27], and TECOS [28]) have not showed CV benefits with DPP-4 inhibitors. In fact, saxagliptin was associated with higher risk of HF [26] and alogliptin [27] showed a trend toward more HF episodes. In contrast, sitagliptin did not increase HF risk [28]. Thus, DPP-4 inhibitors do not provide CV benefits but are considered safe from a CV standpoint (except for saxagliptin, which worsens HF). They are overall considered a second-line option after metformin.

3. SGLT2 inhibitors: pharmacodynamics

Glucose is freely filtered by in the glomerulus and is reabsorbed in the proximal convoluted tubule (PCT). In humans the maximum renal glucose reabsorptive capacity (TmG) is 375 mg/min. In normal-glucose tolerant individuals the rate at which glucose is filtered (180 g/day or 125 mg/minute, assuming normal glomerular filtration rate (eGFR) of 180 L/day with a mean day-long plasma glucose level of 100 mg/dL) is lower than the TmG so all filtered glucose is reabsorbed and there is no glycosuria (Figure 1(a)). In patients with poorly controlled T1DM or T2DM, however, the filtered glucose load exceeds the TmG resulting in glycosuria (Figure 1(b)). In healthy individuals no glycosuria appears until glycemia exceeds 180 mg/dL [36].

Glucose, being a polar compound, cannot permeate through the walls of the PCT so it is reabsorbed with help of glucose transport. Two sodium glucose cotransporters are present in the apical membrane of the PCT. SGLT2 is a high capacity/low affinity cotransporter which is present in the first segment (S1) of the PCT and is responsible for resorption of 90% of the glucose, while is a high-affinity, low-capacity glucose/galactose transporter located on the S2 (later part of the PCT) and S3 segments (proximal straight tubule). The Na/K ATPase pump, presents in the basolateral membrane extrudes, three Na ions from the lumen into the blood and in return it brings in 2 K ions; this leads to a decline in intracellular sodium concentration and the formation of a downhill sodium gradient. The SGLT proteins employ the energy generated by this downhill gradient to transport one glucose molecule against the uphill glucose gradient and Na ion across the apical membrane of PCT. This is an example of secondary active transport. The ratios of sodium to glucose cotransport inside the cell are 1:1 and 2:1 for SGLT2 and SGLT1, respectively [36]. The glucose is then transferred into the blood by GLUT1 and GLUT2 transporters present on the basolateral membrane of PCT [19,36].

Patients and animal models with poorly controlled diabetes have a 20% increase in TmG compared to nondiabetic subjects [36]. This seems to be caused by the increased SGLT2 expression in the PCT of diabetic subjects demonstrated in preliminary studies in animal models [37] and human patients [38], although not all studies confirm this SGLT2 overexpression [39]. In fact, this increase in renal glucose resorption is part of the ominous octet, thus SGLT2 inhibition will decrease renal glucose resorption and will improve glycemic control (e.g. reduction in HbA1c).

The pharmacodynamic effect of SGLT2 inhibitors is inducing glycosuria by decreasing both the TmG and the threshold for glucose resorption. In well-controlled T2DM patients,

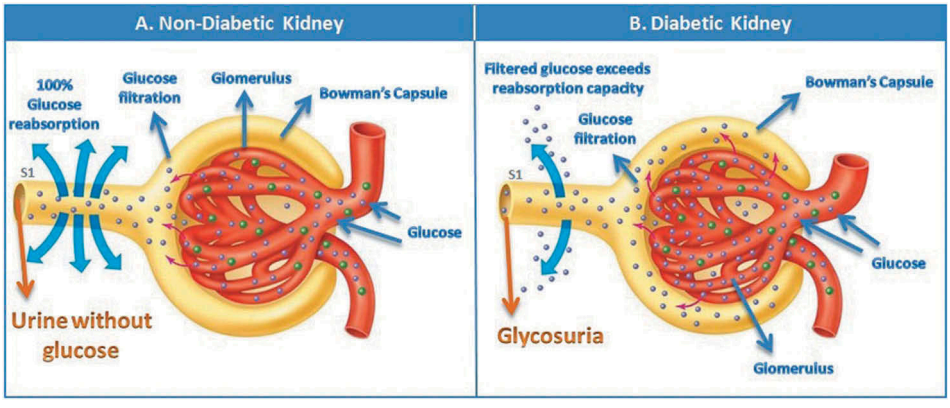

Figure 1. Comparison of renal-glucose filtration and reabsorption process in a non-diabetic individual (A) and in a diabetic individual (B)

dapagliflozin for instance, decreased the TmG by 56% (from 420 mg/min to 184 mg/min) [40]. Nondiabetic patients also show glycosuria despite normal glycemia; this glycosuria in the presence of normal glycemia is explained by a marked reduction in threshold for glucose resorption from 180 mg/dL to 40–80 mg/dL [40–42].

Although SGLT2 mediates the reabsorption of 90% of filtered glucose (160 g/day in healthy individuals), SGLT2 inhibitors only increase urinary glucose excretion by 80 g/day (less than 50% of the filtered glucose load). This paradox is explained by SGLT1. Given its more distal location on S2/S3 and the fact that SGLT2 has already reabsorbed 90% of glucose, SGLT1 operates well below its maximal transport capacity of 80 g/day [43]. SGLT2 inhibition results in the delivery of a large amount of glucose to the SGLT1 transporter, which now can act at full reabsorptive capacity, explaining why less than 50% of filtered glucose appears in the urine. In summary, SGLT2 reabsorbs 90% of the filtered glucose but SGLT1 can reabsorb up to 40% of this filtered glucose [43].

Pharmacokinetics and pharmacodynamics of SGLT2 inhibitors are presented in Table 2.

4. SGLT2 inhibitors: pharmacokinetics

Phlorizin, the first natural SGLT2 inhibitor, was isolated in 1835 from the root bark of the apple tree and discovered to cause glycosuria. Phlorizin was never developed as antihyperglycemic agent because of its rapid oral degradation; it possesses an O-glucoside link that is sensitive to digestive β-glucosidase, which explains its poor gastrointestinal absorption [36]. Other drugs subsequently have been developed and up to date, the only drugs approved by FDA for treating T2DM patients are empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin.

- **Dapagliflozin**: It was the first SGLT2 inhibitor approved in the world (Europe, November 2012; USA January 2014). It is available in monotherapy and combination with metformin and saxagliptin. Initial dose is 5 mg and can be uptitrated to 10 mg. Dapagliflozin is around 1,200 times more selective for SGLT2 than for SLGT1 [44]. Bioavailability of dapagliflozin is 78% and is not altered by a high-fat meal, thus allowing for administration irrespective of meals. Dapagliflozin is rapidly absorbed after oral administration (it reaches maximum plasma levels (T_{max}) 1–1.5 h after administration, it binds 78% to proteins, and the half-life ($T_{1/2}$) is 13 h [45], which makes it appropriate for once-daily dosing. In addition, no interactions with other drugs commonly used in the treatment of T2DM have been reported. It is not recommended for patients with moderate-severe renal impairment, dialysis, ≥ 75 years old, pregnancy, or breastfeeding. In patients with severe hepatic impairment, the medication should be started as 5 mg once daily [46].
- **Canagliflozin**: It was the first SLGT2 inhibitor approved in the United States (March 2013). It is slightly less selective for SGLT2 (250-fold selectivity for SGLT2 over SGLT1). It induces a dose-dependent decrease in the 24 h renal glucose threshold [44]. It is administered once daily before the first meal of the day at starting dose of 100 mg, that can be uptitrated to 300 mg daily. The absolute bioavailability of canagliflozin is 65% (300 mg dose), and it is tightly bound to plasma proteins (99%). Canagliflozin peak plasma levels are attained within 1–2 h and the apparent terminal half-life is 11 h (for 100 mg dose) and 13 h (for 300 mg dose), respectively [45]. No significant interactions with other drugs have been reported. Canagliflozin is not recommended in patients with eGFR < 45 mL/min/1.73 m^2 and severe hepatic impairment. It is considered category C agent for pregnant women. In older population, 100 mg may be considered the maximum daily dose.
- **Empagliflozin**: Empagliflozin was approved in 2014 (May 2014 in Europe, August 2014 in USA). Empagliflozin is the SGLT2 inhibitor with the highest selectivity for SGLT2 over SGLT1 (>2,500-fold). It is also available as a combination product with Metformin and Linagliptin. The recommended dose is 10 mg, once daily in the morning, with or without food, and can be titrated up to 25 mg once daily. There are only preliminary data about the bioavailability of empagliflozin, which seems to be around 75%, and it can be taken before or after meals. Empagliflozin is rapidly absorbed after oral administration (T_{max} 1.5 h), it binds to proteins by 86%, and the half-life ($T_{1/2}$) is 13 h [45], which makes it appropriate for once-daily dosing. In addition, no interactions with other drugs commonly used in the treatment of T2DM have been reported. Empagliflozin is eliminated both by the fecal (40%) and renal (55%) routes. Empagliflozin is well tolerated in chronic kidney disease (stages 2–3), and only induces some hypoglycemia in stage 4. It is not recommended during pregnancy or breastfeeding.
- **Ertugliflozin**: It is the newest SGLT2 inhibitor approved by the FDA. Sparse data yet exist regarding pharmacokinetics and pharmacodynamics of this drug. Initial recommended dose is 5 mg once daily, taken in the morning with or without food, and it can be titrated up to 15 mg once daily. Its bioavailability can rise up to 90% after oral administration and it has both renal and fecal elimination, approximately equal in percentage. Serious drug-to drug interactions have not been reported and it presents a similar contraindication and precaution profile to other SGLT2 inhibitors. Ertugliflozin should not be started in patients with eGFR < 60 mL/min/1.73 m^2 and is contraindicated if eGFR < 30 mL/min/1.73 m^2 [47].
- **Sotagliflozin**: It is the first dual SGLT1/SGLT2 inhibitor to reach phase-III trials. It has a slightly greater affinity for SGLT-2 receptor over SGLT-1 (only 20-fold) [48]. Dosing directly before breakfast has shown to maximize its effects. The increase in 24-h urinary glucose excretion relative to baseline seems to be modest as compared with only SGLT2 inhibition (probably as a result of the additional intestinal glucose absorption inhibition by SGLT1 inhibitor effect). Sotagliflozin has a dose-dependent effect except for the urinary glucose excretion, which has a plateau from the 200 mg once daily dose onward [48]. The T_{max} is 3 h, with up to 97.7% of plasma protein binding. It has a rapid onset of absorption and a $T_{1/2}$ between 13.5 and 20.7 h in T2DM patients with normal renal function, suggesting the appropriateness of once-daily dosing. Despite its predominantly

Table 2. Pharmacokinetics and pharmacodynamics of SGLT2 inhibitors.

SGLT2 inhibitor	Approval	Route	Dose and dose interval	Mixture products	Bioavailability	Time to peak action/ Half-life	Excretion	Interactions	Contraindications
Empagliflozin	EMA FDA	Oral	• Initial dose 10 mg OD • Titration up to 25 mg OD	• With Linagliptin • With Metformin	~75%	1.5 h/13 h	Renal (55%) Fecal (40%)	No significant with other drugs commonly used in T2DM	• Hypersensitivity • Severe renal impairment, ESRD, or dialysis • Pregnancy or breastfeeding
Canagliflozin	EMA FDA	Oral	• Initial dose 100 mg OD • Titration up to 300 mg OD	• With Metformin	~65%	1–2 h/11–13 h	Fecal (41.5%) Renal (33%)	No significant with other drugs commonly used in T2DM	• Hypersensitivity • Severe renal impairment, ESRD, or dialysis • Pregnancy or breastfeeding (precaution)
Dapagliflozin	EMA FDA	Oral	• Initial dose 5 mg OD • Titration up to 10 mg OD	• With Saxagliptin • With Metformin	~78%	1–1.5 h/13 h	Renal (75%) Fecal (21%)	No significant with other drugs commonly used in T2DM	• Hypersensitivity • Severe renal impairment, ESRD, or dialysis • Pregnancy or breastfeeding (precaution)
Ertugliflozin	EMA FDA	Oral	• Initial dose 5 mg OD • Titration up to 15 mg OD	• With Sitagliptin • With Metformin	70–90%	0.5–1.5 h/11–17 h	Renal (50%) Fecal (41%)	No significant with other drugs commonly used in T2DM	• Hypersensitivity • Severe renal impairment, ESRD, or dialysis • Pregnancy or breastfeeding (precaution)
Ipragliflozin	Japan	Oral	• Initial dose 50 mg OD • Titration up to 100 mg OD	• With Sitagliptin • With Metformin	~90%	1.5 h/15–16 h	Fecal (~100%) Renal (<2%)	No significant with other drugs commonly used in T2DM	• Hypersensitivity • Severe renal impairment, ESRD, or dialysis • Pregnancy or breastfeeding (precaution)
Tofogliflozin	Japan	Oral	• Initial dose 20 mg OD • Titration up to 40 mg OD	–	97.5%	0.5–1.5 h/5–6 h	Renal (76%) Fecal (20%)	No significant with other drugs commonly used in T2DM	• Hypersensitivity • Severe renal impairment, ESRD, or dialysis • Pregnancy or breastfeeding (precaution)
Sotagliflozin	Under investigation	Oral	• Initial dose 200 mg OD • Titration up to 400 mg OD	–	–	3 h/13.5–20.7 h	Mostly renal	–	–

EMA: European Medicines Agency; ESRD: end-stage renal disease; FDA: Food and Drug Administration; h: hours; OD: once daily; T2DM: type 2 diabetes mellitus.

renal clearance route, plasma elimination of sotagliflozin is not substantially altered in patients with kidney disease [48]. The inTANDEM trials [48,49] studied 1,406 patients with T1DM randomized to sotagliflozin 400 mg or placebo. The primary endpoint (percentage of patients achieving HbA1c < 7% without episodes of hypoglycemia or DKA) was higher in the sotagliflozin group. Sotagliflozin also reduced HbA1c and insulin doses without inducing overall hypoglycemia. These results will probably propel the drug toward regulatory consideration for T1DM patients. The rates of adverse events were higher with sotagliflozin than with placebo, particularly in those subjects receiving the higher dose (400 mg daily). Nausea, diarrhea, and genitourinary were the most commons (as expected due to intestinal SGLT1 inhibition). This trial also showed a dose-dependent trend to higher rates of diabetic ketoacidosis (DKA), which are even greater in insulin pump users. Hypoglycemic events did not differ between groups, except for insulin pump users, that presented increased rates of severe hypoglycemia.

- **Other SGLT inhibitors**: Additional SLGT2 inhibitors are sergliflozin, remogliflozin, ipragliflozin, and tofogliflozin. The first one is remarked by a very short half-life (<2 h) and does not accumulate in the body fluids. Neither sergliflozin nor remogliflozin has been developed for clinical use (probably because they contain O-glucoside linkages that render them susceptible to hydrolysis by β-glucosidases) [44]. Ipragliflozin and tofogliflozin are approved only in Japan [50,51] and their pharmacological profile is displayed also in Table 2.

5. Other effects of SGLT2 inhibitors

An overview of SGLT2 inhibitors effects is presented in Figure 2. All the four approved SGLT2 inhibitors have shown to produce weight loss when compared to placebo in both, monotherapy and in combination with other antidiabetic agents. Empagliflozin was also superior to metformin in achieving this weight loss [46]. The increase in urinary glucose excretion is around 60 g of glucose per day, i.e. around 240 calories daily and 3,600 calories in 2 weeks, which causes a weight loss of almost 0.5 Kg. Hence, this weight loss seems to be predominantly attributable to reductions in body fat mass secondary to increased lipolysis and fatty acid oxidation, and reductions in visceral fat has been reported in T2DM patients treated with SGLT2 inhibitors [52]. There is an average weight loss of 2–3 kg that occurs gradually over the first few months on treatment, and it appears to reach a nadir and thereafter stabilizes after 3–6 months [53,54]. This plateau may be due to increase in caloric intake as demonstrated in humans [55], so the combination of GLP-1 mimetic and SGLT2 inhibitor seems highly attractive.

In addition, patients treated with SGLT2 inhibitors showed a consistent small decrease in blood pressure (BP), with systolic BP reduction between 3 and 6 mmHg. As sodium and glucose are cotransported in the proximal tubule, the enhanced glucose reabsorption in diabetic patients (part of the ominous octet) causes reduced natriuresis, increased total body sodium, and hence eventual hypertension. Therefore, SGLT2 inhibition causes a direct natriuretic effect that reduces BP. There is a second mechanism explaining the reduced BP, namely osmotic diuresis secondary to high glucose concentration in the urine with reduction in plasma volume. A third mechanism may also play a potential role: the sodium-hydrogen exchanger 3 (NHE3) is highly expressed in the apical surface of renal epithelial cells and is responsible for a majority of the sodium reuptake that follows glomerular filtration [56]; SLGT2 inhibitors also block NHE3 [57], which causes reduced sodium reabsorption and increased natriuresis [56]. This antihypertensive effects occurred without compensatory increase in heart rate, suggesting a lack of compensatory sympathetic activation [53].

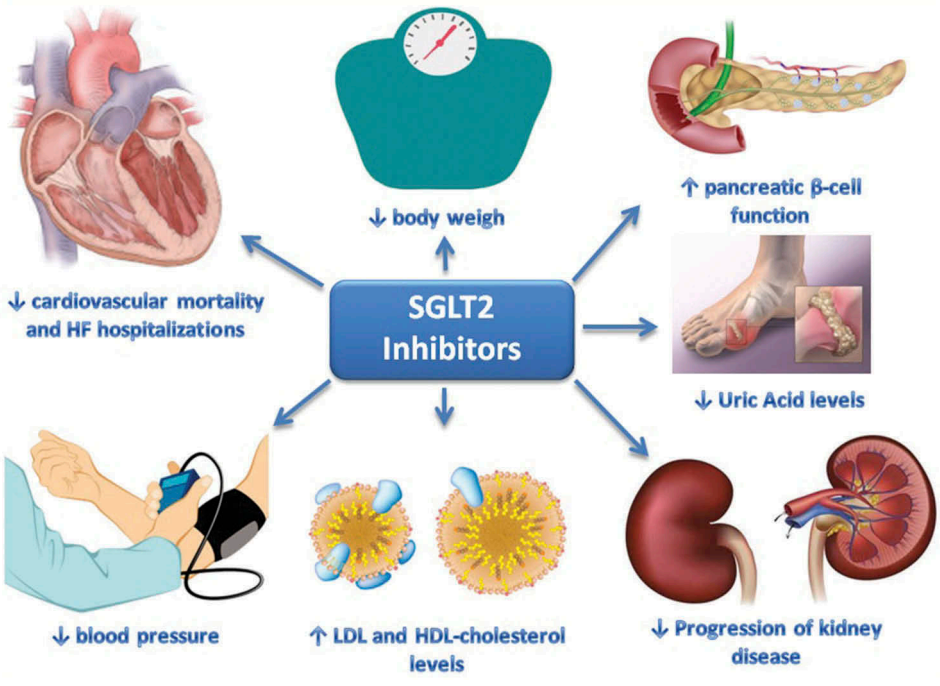

Figure 2. Overview of the SGLT2 inhibitors systemic effects.

Furthermore, SGLT2 inhibition enhances β-cell function, which also contributes to improved glycemic control. Treatment with dapagliflozin [58] or empagliflozin [59] results in augmented β-cell glucose sensitivity and improved β-cell function. Despite the lack of direct effect on β-cell, this improvement is likely to be secondary to reduction of the plasma glucose concentration and amelioration of glucotoxicity.

Changes in lipid levels have also been reported. SGLT2 inhibitors cause 5% increase in LDL-C and 5–8% in HDL-C, with a 5% decrease in triglyceride levels [36]. The small rise in LDL-C concentrations might be secondary to a reduction in LDL catabolism because the expression of hepatic LDL receptors is decreased by 20% under SGLT2 inhibitors [60]. However, as shown in EMPA-REG OUTCOME trial, this does not cause any increase in CV events [61].

6. Efficacy of SGLT2 inhibitors in diabetes mellitus

The only SGLT2 inhibitors approved by the Food and Drug Administration (FDA) are empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin.

- **Empagliflozin**: It improves glucose control in T2DM patients. It reduces significantly HbA1c levels and fasting plasma glucose (FPG) levels versus placebo [62]. Across all published studies, the maximum decrease in HbA1c level was 1% from baseline [46]. For instance, in a placebo and active comparator controlled trial, 899 patients were randomized to receive empagliflozin 10 or 25 mg, sitagliptin and placebo. Compared with placebo, after 24 weeks of treatment, mean differences in change from baseline HbA1c were −0.73% for sitagliptin, −0.74% for empagliflozin 10 mg, and −0.85% for empagliflozin 25 mg [46,63]. Empagliflozin also showed to be beneficial as a second drug (in combination with metformin) and as a third drug (when added to metformin and SFUs) [54,64]. Regarding combination with insulin, empagliflozin showed not only a significant lowering of HbA1c levels, but also a reduction in insulin dose, as compared to placebo [65].
- **Canagliflozin**: It has been studied as monotherapy or in combination either with one or two more antidiabetic drugs. In drug-naïve patients, canagliflozin has significant benefit in lowering HbA1c levels as well as FPG and postprandial glycemic parameters [66], likely also inhibiting SGLT2 receptor and thus delaying intestinal glucose absorption [67]. The maximum reduction in HbA1c levels from baseline was ~ 1% [46]. In studies that have analyzed the combination of metformin + canagliflozin, there has also been a significant benefit in HbA1c levels as compared to either placebo or sitagliptin, and was noninferior to metformin + glimepiride [68,69]. When in combination with SFUs, DPP-4 inhibitors or insulin, canagliflozin versus placebo seems to be beneficial as well [70,71]. Additionally, this benefit was hold when used as a third medication [72].
- **Dapagliflozin**: Several studies have proved its effectiveness in lowering HbA1c both, in monotherapy trials and in add-on trials. When compared to placebo in drug-naïve patients, dapagliflozin significantly reduced HbA1c blood levels and FPG [73–75]. The maximum decrease in HbA1c levels was 1.45% [46]. In addition, dapagliflozin, at dose 10 mg/day, was noninferior to metformin in reducing HbA1c levels and was superior in reducing FPG [76]. Dapagliflozin added to other glucose-lowering drugs (metformin, glimepiride, pioglitazone, sitagliptin, and insulin) has also showed a significant decreased in HbAa1c levels, as compared to placebo [77–80]. Moreover, the combination of both metformin and dapagliflozin in naïve-patients has demonstrated more effectiveness in decreasing HbA1c levels than either drug alone [76].
- **Ertugliflozin**: This new antidiabetic drug was approved by FDA in December 2017. Few clinical trials have studied ertugliflozin in T2DM patients. VERTIS MONO, VERTIS MET, and VERTIS SITA [81–83] have showed that ertugliflozin significantly lowers HbA1c levels in monotherapy and in combination with metformin and sitagliptin, respectively, when compared with placebo. The maximum decrease in HbA1c levels was 1.7%.

6.1. Global perspective

Data regarding the efficacy of these three SGLT2 inhibitors approved for T2DM patients, were published in 2016 in a meta-analysis including a total of near 24,000 patients from 38 trials [84]. A significant reduction in HbA1c levels was seen in every single drug (from a maximum of −0.9% for canagliflozin 300 mg, to −0.7% for empagliflozin 25 mg, down to −0.6% with dapagliflozin 5 mg) against placebo. The pairwise random-effects meta-analysis showed controversial results when analyzing SLTG2 inhibitors and other glucose-lowering drugs (including DDP inhibitors, SFUs and metformin). Dapagliflozin presented significant greater reduction in HbA1c levels comparing to DPP-4 inhibitors and SFUs but not to metformin. Empagliflozin was only superior to SFUs; and there are no conclusive data regarding canagliflozin. These SGLT2 inhibitors seem to decrease HbA1c levels greater when used at higher doses (canagliflozin 300 mg vs 100 mg; empagliflozin 25 mg vs 10 mg; and dapagliflozin 10 mg vs 5 mg). No further studies have been yet published contrasting different SGLT2 inhibitors.

7. Efficacy of SGLT2 inhibitors in cardiology

There is a greater risk for HF in T2DM patients (twofold increase in men and up to fivefold increase in women). This association is due to a metabolic, functional and structural impairment (the so called 'diabetic cardiomyopathy'). Hyperglycemia might cause microvascular damage, thus cardiac remodeling and fibrosis; it is also associated with mitochondrial dysfunction that may impair myocardial contractility and changes in the extracellular matrix that increase stiffness and affect diastolic function [62]. The main characteristics and outcomes of the four FDA-approved SLGT2 inhibitors are presented in Table 3.

Table 3. Safety and effectiveness of FDA-approved SGLT2 inhibitors.

SGLT2 inhibitor	T2DM	CV outcomes	Renal outcomes	Additional effects	Recommended dose and adverse effects
Empagliflozin	• Maximum HbA1c lowering < 1% • Effective in mono-therapy and in combination	• Significant ↓ of CV death (RRR of 38%), hospitalization for HF (RRR of 35%) and death from any cause (RRR 32%) (EMPA-REG-OUTCOME) • Two ongoing trials: EMPEROR-reduced and EMPEROR-preserved (for CV outcomes in HFrEF and HFpEF, respectively)	• ↓ Progression of kidney disease (RRR of 44% for doubling serum creatinine)	• B-cell function improvement • Weight loss • Natriuretic • ↓ SBP • ↓ Acid uric • Small ↑ in HDL-c and LDL-c	• Dose: 10 mg/d (up to 25 mg/d) • It may cause genitourinary tract infections • Hypoglycemia infrequent
Canagliflozin	• Maximum HbA1c lowering ≈1% • Effective in mono-therapy and in combination	• Significant ↓ of hospitalization for HF (RRR of 33%) and death from any cause (RRR 13%) (CANVAS PROGRAM) • CREDENCE: ongoing trial on CV and renal outcomes.	• It may ↓ progression of kidney disease (RRR of 27% for progression of albuminuria)	• Weight loss • Natriuretic • ↓ SBP • ↓ Acid uric • Small ↑ in HDL-c and LDL-c	• Dose: 100 mg/d (up to 300 mg/d) • It may cause genitourinary tract infections • Hypoglycemia may be greater than dapagliflozin or empagliflozin • Significant ↑ of lower extremity amputations
Dapagliflozin	• Maximum HbA1c lowering 1.45% • Effective in mono-therapy and in combination	• No CV outcomes yet available • Two ongoing trials: DECLARE-TIMI 38 (for CV outcomes) and DAPA-HF (in HFrEF patients)	• It may ↓ progression of kidney disease (scarce date yet)	• Weight loss • Natriuretic • ↓ SBP • ↓ Acid uric • Small ↑ in HDL-c and LDL-c	• Dose: 10 mg/d • Most frequent AE: headache and diarrhea • It may cause genitourinary tract infections • Hypoglycemia infrequent • It may Increase breast and bladder cancer rates (unknown mechanism)
Ertugliflozin	• Maximum HbA1c lowering 1.7% • Approved in December 2017	• No CV outcomes yet available	• No renal outcomes yet available	• Probably same additional effects as	• Dose: 5 mg/d (up to 15 mg/d) • It may cause Genitourinary tract infections • Hypoglycemia infrequent

AE: adverse events; CV: cardiovascular; EP: end point; HF: heart failure; HDL-c: high-density lipoprotein cholesterol; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LDL-c: low density lipoprotein cholesterol; MI: myocardial infarction; RRR: relative risk reduction; SBP: systolic blood pressure

- **Empagliflozin**: The EMPA-REG OUTCOME clinical trial [61] was the first trial on CV morbidity and mortality in T2DM patients that included a high-risk CV population (all patients had established CV disease, 10% of them with prior history of HF). A total of 7,020 T2DM patients were randomly assigned to receive either empagliflozin (10 or 25 mg) or placebo. The median observation time was 3.1 years and the primary composite end point was three-point MACE (CV death, nonfatal MI, or nonfatal stroke). The study showed significantly lower rates of the primary endpoint in the pooled empagliflozin group compared with placebo (HR 0.86, 95% CI [0.74–0.99]). There was no significant reduction in the rates of MI or stroke. Of the outmost importance, empagliflozin reduced CV death by 38%, total death by 32%, and hospitalization for HF by 32%. Interestingly, empagliflozin has showed to reduce the incidence of CV death and HF hospitalization across all spectrum of HF severity [85], including patients at both high and low risk of HF (HR for patients at low-to-average risk 0.71, 95% CI [0.52–0.96]; patients at high risk of HF 0.52, 95% CI [0.36–0.75] and patients at very high risk of HF 0.55, 95% CI [0.30–1.00]). Furthermore, empagliflozin also improved clinical outcomes and reduced mortality in T2DM patients with established CV disease and chronic kidney disease [86]. Currently, there are two additional ongoing trials investigating empagliflozin and CV outcomes in patients with HF and reduced ejection fraction (EF), EMPEROR-Reduced (NCT 03057977); and in those with preserved EF, EMPEROR-Preserved (NCT 03057951). An additional clinical trial, EMPATROPISM (NCT 03485222), specifically investigates the efficacy and safety of empagliflozin in nondiabetic HF patients.
- **Canagliflozin**: This drug has been tested in T2DM patients for both, primary and secondary CV prevention in the CANVAS program [87]. In the pooled cohort, the primary end point of three-point MACE was significantly reduced with canagliflozin compared to placebo. In addition, there was no statistical evidence of heterogenicity between the primary and secondary prevention groups. Interestingly, a significant decreased for the secondary end point (i.e. HF hospitalization or a renal composite end point) was also observed in both primary and secondary prevention groups as compared to placebo. The results of CANVAS confirm the CV benefits of SGLT2 inhibitors. However, these benefit appears to be lower as compared to empagliflozin in the EMPA-REG OUTCOME (HR for death from CV causes: 0.62, 95% CI [0.49–0.77] for empagliflozin trial and 0.87, 95% CI [0.72–1.06] for canagliflozin trial; HR for hospitalization for HF: 0.65, 95% CI [0.50–0.85] for empagliflozin and 0.67, 95% CI [0.52–0.87]. However, in a large cohort study, canagliflozin demonstrated lower risk of HF hospitalizations when compared to other antidiabetic drugs, including DPP-4 inhibitors, GLP-1RA and SFUs [88]. Further studies with canagliflozin are ongoing, such as the CREDENCE trial (NCT02065791) investigating the effects of canagliflozin on CV and renal outcomes.
- **Dapagliflozin**: The use of dapagliflozin in T2DM patients and risk for CVD has been recently investigated in the DECLARE-TIMI 58 trial [89]. Over 17,000 participants were including in the study (7,000 of them with established atherosclerotic cardiovascular disease). They were randomized to dapagliflozin vs. placebo on top of optimal medical therapy. Although for the primary composite endpoint of MACE dapagliflozin did not show differences compared with placebo, for the coprimary endpoint of CV death or hospitalization for HF dapagliflozin significantly demonstrated benefits (HR for CV death or hospitalization for HF 0.83, 95% CI [0.73–0.95]). There is another ongoing trial, DAPA-HF (NCT03036124) analyzing the effect of dapagliflozin in HF patients with reduced ejection fraction.

In summary, SGLT2 inhibitors have showed to reduce the risk of HF episodes as compared to both DPP-4 inhibitors and GLP1-RA and, additionally, SGLT2 along with GLP1-RA reduce mortality in T2DM patients as compared to DPP-4 inhibitors [88,90].

8. Efficacy of SGLT2 inhibitors in renal function

- **Empagliflozin**: In the EMPA-REG OUTCOME trial, empagliflozin reduced the progression of kidney disease [91]. The hazard ratio for incident or worsening nephropathy for empagliflozin as compared to placebo was 0.61, 95% CI [0.53–0.70]. There was a significant risk reduction of 44% for doubling serum creatinine level and a significant risk reduction of 55% for requiring renal-replacement therapy in the empagliflozin group as compared to placebo group. Patients in the empagliflozin group also had a lower risk of progression to microalbuminuria [91]. The mechanisms behind the renal effects of empagliflozin are probably multifactorial, including amelioration of glucotoxicity but also a direct renovascular effect. In poorly controlled T2DM patients, filtered glucose load is increased and glucose along with sodium reabsorption is increased in the PCT by both SGLT2 and SGLT1. This reabsorption reduces sodium delivery to the juxtaglomerular apparatus, making the kidney seemed underperfused. These effects lead to local release of renin and angiotensin, resulting in constriction of the adjacent efferent arteriole, and dilation of the afferent arteriole; the net result is an increase in intraglomerular pressure and GFR which causes glomerular damage in the long term. SGLT2 inhibition increases the delivery of sodium to the juxtaglomerular apparatus leading to afferent arteriole constriction, decreased intraglomerular pressure, and normalization of GFR to normal [36].
- **Canagliflozin**: Results from the CANVAS program, including CANVAS-R [87] showed a probable benefit of canagliflozin with respect to the progression of albuminuria versus placebo (HR 0.73, 95% CI [0.67–0.79]) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal cause (HR 0.60, 95% CI [0.47–0.77]). However, on the basis of the prespecified hypothesis testing sequence, the renal outcomes are not viewed as statistically significant.

- **Dapagliflozin**: This agent may exhibit also renal benefits. In a post hoc analysis of a cross-over trial, dapagliflozin decreased albuminuria by 44% (95% CI [30.3–54.8%]) [92].

9. Suggested mechanism underlying cardiovascular benefits of SGLT2 inhibitors

The mechanisms explaining the CV benefits of SGLT2 inhibitors in EMPA-REG OUTCOME trial, CANVAS trial and DECLARE-TIMI 58 are not completely understood. The glucose-lowering effects of SGLT2 inhibitors seem unlikely to explain these benefits since differences in HbA1c were (by design) minimal, improvement in glycemic control should translate into reduced incidence of MI/stroke (which were not different between arms), it takes years to show the benefits of glucose control, and still tight glycemic control has previously failed to reduce either mortality or HF [6,93]. Additional mechanisms associated with SLGT2 inhibitors may play a role on CV findings. These include antioxidative, antiinflammatory, or antiapoptotic properties attributed to these medications. In addition, SGLT2 inhibitors induce the secretion of glucagon, a molecule with known inotropic effects that increases myocardial contractility [94].

9.1. Sodium-hydrogen exchanger (NHE)

The sodium-hydrogen exchanger (NHE) is receiving lot of attention. There are more than nine related NHE isoforms. NHE1, that regulates cardiomyocyte pH and volume and protects against ischemia-reperfusion injury, is predominantly in the heart. Importantly, norepinephrine, angiotensin, and aldosterone, whose concentrations are increased in HF and T2DM patients, stimulate activity of NHE1 in the heart and of both NHE1 and NHE3 in the kidneys [56]. An increased in myocardial anaerobic metabolism (due to cardiac overload in HF) generates certain degree of lactic acidosis. As a consequence of the drop in intracellular pH there is an upregulation of NHE1 activity that produces an increase of intracellular sodium and therefore, a reversal of the Na^+/Ca^+ exchanger activity. The ultimate effect is an increase on intracellular calcium that triggers cardiomyocyte injury and cell death. SGLT2 inhibitors have been demonstrated to inhibit NHE1 [57,95], which can theoretically ameliorate cardiac injury by reducing cardiac necrosis, fibrosis, and remodeling. However, another NHE1 inhibitor cariporide previously failed to show benefits in human patients [96] so there are probably additional mechanisms.

9.2. Improved myocardial metabolism

Abnormalities in myocardial energy metabolism precede and contribute to HF [97,98]. The high-energy demands of healthy myocardium are primarily met by the mitochondrial oxidation of free fatty acids (FFA); however, the heart possesses metabolic flexibility, which allows utilization of different substrates (including glucose, ketones, and lactate) according to workload and substrate availability. FFAs are the preferred myocardial fuel for oxidative metabolism because complete oxidation of one palmitate molecule generates more ATP (energy liberated 298 kcal/mol), but this is at the expense of high oxygen requirements (P/O ratio—meaning number of ATP molecules produced per oxygen atom reduced by the mitochondria—for palmitate is 2.33) [99,100]. Under hypoxic conditions such as the increased workload found in HF, myocardial substrate oxidation switches from fat to carbohydrate oxidation (fetal-like metabolism); glucose becomes the preferred substrate because it is more oxygen-efficient (P/O ratio 2.58) than FFA oxidation [99,100], but this is at the expense of lower energy produced (energy liberated 224 kcal/mol). This shift in myocardial metabolism from FFA to glucose consumption creates an energy deficit [97] that impairs cardiac efficiency and aggravates HF. Importantly, ketones are the most energetically efficient fuel (energy liberated 244 kcal/mL with a P/O ratio of 2.5) [99,100]. In fact, when ketones are added to the perfusion medium of working rat hearts, the heat of combustion per unit of carbon increases by 31% and myocardial efficiency improves by 27%.

Of note, empagliflozin-induced glycosuria reduces both plasma glucose and insulin levels while increases both lipolysis and plasma glucagon concentration, which causes ketogenesis and hyperketonemia [101,102]; this pattern is similar to that of fasting except that fasting develops slower. Given that SGLT2 inhibition causes mild, persistent hyperketonemia, and that myocardial ketone bodies uptake is in proportion to their plasma concentration [103], we and others have hypothesized that the cardiac benefits of empagliflozin are due to a metabolic switch in myocardial fuel utilization away from glucose oxidation, which is energy-inefficient in the setting of HF, toward ketones, which are more energy-efficient and thus improving myocardial work efficiency. In fact, we have recently demonstrated this hypothesis in a porcine model of HF [104]; pigs with HF treated with empagliflozin exhibited myocardial ketone consumption while cardiac glucose utilization was minimized, which resulted in ameliorated HF, less cardiac remodeling, augmented systolic function and enhanced myocardial efficiency.

9.3. Improved cardiovascular function

Mechanistic human data related to antihypertensive effects of these agents remain limited. The blood pressure lowering effect of SGLT2 inhibition may be related to several mechanism including diuretic effects, changes in neurohormonal activation, improved glycemic control and body weight loss. In addition, arterial stiffness increases under the influence of ambient hyperglycemia and can be improved through tight glycemic control. In this regard, empagliflozin, for instance has demonstrated to have favorable effects on markers of arterial stiffness and vascular resistance [105,106]. Furthermore, SGLT2 inhibitors may elicit a direct cardiac effect since they have shown to increase cardiac relaxation, improve diastolic function and cardiac biomarkers [107–110]. All this results suggest additional benefits other than via SGLT2 receptor blockage since the human heart does not express this receptor.

9.4. Diuretic effects

SGLT2 inhibitors primarily act on the proximal tubules causing osmotic diuresis. However, this osmotic effect is quantitatively small. Thus, the diuretic effect observed with these agents

may be related to direct action in the loop of Henle rather than in proximal tubules. It is well known that diuretic therapy has remarkable effects on preventing HF and stroke. In addition, SGLT2 do not cause hypokalemia. This diuretic effect would also be playing a significant role on improving CV outcomes observed with this drugs [111].

10. Safety of SGLT2 inhibitors

Clinically, the most relevant side effect of SGLT2 inhibitors is an increase in genitourinary infections, which are more common in women and under susceptible conditions such as postmenopausal women and those with prior history of urinary tract infections [19,45,46]. Most infections were mild-to-moderate in intensity and responded to a course of standard treatment. Infections of the upper urinary tract do not seem to be increased, only mycotic genital infections [45].

Interestingly, hypoglycemia does not seem to occur with the use of SGLT2 inhibitors alone either in patients with T2DM or in nondiabetic individuals because there is an increased in endogenous glucose production in the liver. However, precautions should be taken when in combination with other antidiabetic drugs.

Their mild diuretic effect may slightly increase the risk of orthostatic hypotension, postural dizziness, and dehydration (specially in older patients or with concomitant use of loop diuretics) [46]. In addition, this osmotic diuresis (excess urine volume up to 200–600 mL/day) may lead to an increase in hematocrit and thus, an increase in blood viscosity and thrombogenicity. A tendency toward an increased risk of stroke rates arose from the EMPA-REG OUTCOMES trial (p = 0.2). A clear explanation underlying this finding has not been identified yet. Some suggested hypothesis may be related to a body fluid volume contraction [111] following a massive diuresis in patients with concomitant diuretics (43.7% of the patients in the SGLT2 inhibitor group of the EMPA-REG OUTCOME trial were treated in combination with diuretics). In contrast, some data did not confirm this increase in blood thrombogenicity [112].

Concerns were initially raised regarding a potential increase in the risk of diabetic ketoacidosis (DKA) associated with SGLT2 inhibitors, particularly euglycemic DKA. In a cohort study including 56,325 patients receiving SGLT2 inhibitors, the risk of hospitalization for DKA was not superior as compared with DPP-4 inhibitor users (hazard ratio 0.956, 95% CI [0.581–1.572]) [113]. However, such life-threatened complication should not be ignored and taking into consideration when SGLT2 are used. Specific drug-related side effects are described below.

- **Dapagliflozin**: This SGLT2 inhibitor is well tolerated both as monotherapy and as an add-on to other antidiabetic drugs. The most frequent adverse events were headache and diarrhea, but without significant difference across treatment arms. Dropouts due to adverse events were rare. Hypoglycemic events were infrequent and not statistically significant from placebo group except for when it was combined with insulin or glimepiride [46]. In a recent meta-analysis, dapagliflozin 10 mg seems to increase the risk of urinary infection compared with placebo and empagliflozin [84]. Surprisingly, an increased number of breast and bladder cancers were reported among T2DM treated with dapagliflozin [46]. However, most of the cases of bladder cancer had hematuria at baseline, suggesting a possible preexisting cancer. Even so, dapagliflozin is not currently recommended for patients with bladder cancer.
- **Canagliflozin**: Generally, well tolerated, the incidence of serious adverse events with canagliflozin was compared to control groups [46]. The results from a meta-analysis showed an increased risk of hypoglycemia with both canagliflozin 100 and 300 mg compared with placebo but also compared with dapagliflozin 10 mg and empagliflozin 10 mg [84]. The most common adverse events were female genital mycotic infections and urinary tract infections. Of interest, small reductions in bone density were observed in older patients receiving canagliflozin [46]. Unexpectedly, a significant increased risk of lower extremity amputations has been reported with canagliflozin in the pooled CANVAS program. Lower extremity amputations were similarly increased in the secondary and primary prevention cohorts (HR, 2.07; 95% CI, 1.43–3.00 versus HR, 1.52; 95% CI, 0.70–3.29). The underlying mechanism remains unclear and under further investigations. However, there is a need for clarifying such adverse events observed in patients treated with canagliflozin. Perhaps, a more appropriate statistical consideration should be done, taking into account individual clinical course potentially involved in the diabetes-related amputation. A reduction in the hard-end points by canagliflozin may result in an alternate increase in the other diabetes-related complications, including amputations. Furthermore, if amputation occurred after stopping canagliflozin, this rise in the incidence of amputations may have been caused by worsened glycemic control [114]. Therefore, a more detailed approach should be considered. On the other hand, risk of amputation do not seem to be increased with other SGLT2 inhibitors [115].

11. Expert opinion

As discussed before, SGLT2 inhibitors represent a novel and noteworthy treatment for lowering glucose plasma levels and improving glycemic control in T2DM patients. SGLT2 inhibitors have demonstrated safety and effectiveness for treating T2DM patients both in monotherapy and in combination with other antidiabetic drugs.

Surprisingly, positive results have been found regarding CV outcomes as empagliflozin and canagliflozin improve cardiac prognosis. Empagliflozin has shown to significantly reduced total mortality, cardiac mortality, and HF hospitalizations among patients with T2DM that were at high CV risk (EMPA-REG OUTCOME study); canagliflozin in the CANVAS study also demonstrated to improve cardiac prognosis and reduce HF hospitalizations; and finally the recent publication of the DECLARE-TIMI 58 has also showed positive cardiac effects with dapagliflozin. Therefore, SGLT2 inhibitors may play a role in heart remodeling beyond optimal glucose control, that remains still unclear.

Given these improvements in HF hospitalizations in this safety trial of T2DM patients, there is currently great interest in the investigation of SGLT2 inhibitors as an additional treatment

for HF patients. The EMPEROR trials are currently investigating the efficacy of empagliflozin specifically on HF patients, both in HF with preserved and reduced ejection fraction. If these trials are positive, the use of SGLT2 inhibitors could revolutionize the treatment of HF and improve outcomes. Likewise, the DAPA-HF trial will add more data to understand the surprising cardiac findings observed with these antidiabetic agents.

The underlying mechanism is still unclear. Recent data have demonstrated the existence of a metabolic shift in myocardial fuel consumption away from the energy-inefficient glucose toward ketone bodies, which are more energetically efficient. This mechanism occurs secondary to SGLT2 inhibition-induced glycosuria, reduction in insulin, increase in glucagon, and activation of lipolysis. Some other potential mechanisms including diuretic and antihypertensive effects along with various phisyopathological pathways are under further evaluation. As a consequence, both diabetic and nondiabetic patients may benefit from SGLT2 inhibition since these agents exert properties regardless of their diabetic status. According to this, the EMPATROPISM clinical trial is currently investigating the efficacy and safety of empagliflozin in nondiabetic HF patients. If this trial is positive, then empagliflozin could be considered as an alternative in HF patients independently of the diabetic status of the patient.

Other areas of interest for SGLT2 inhibitors are obesity and nonalcoholic fatty liver disease (NAFLD). As SGLT2 inhibitors cause lipolysis, the first fat deposits to be mobilized will be intraabdominal visceral fat and liver fat. For obesity, SGLT2 inhibitors cause weight loss and will reduce visceral fat (the main source of proinflammatory cytokines), which will improve glucose control and obesity-related comorbidities. Also, there is currently no efficacious treatment of NAFLD; as SGLT2 inhibition will burn intrahepatic fat, there will theoretically be a marked improvement in NAFLD.

In summary, SGLT2 inhibitors cannot be considered exclusively as antidiabetic drugs. They offer positive effects in the whole body and it is likely that in the future they will be effective treatments for HF, renal dysfunction, NAFLD, and obesity

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