SGLT-2 inhibitors for the treatment of type-2 diabetes in heart failure patients

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SGLT2 INHIBITORS FOR THE TREATMENT OF TYPE-2 DIABETES IN HEART FAILURE

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Summary

Title: SGLT2 Inhibitors for the Treatment of Type-2 Diabetes in Heart Failure

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In this literature review we have summarised the types of Sglt-2 inhibitors for the treatment of type-2 diabetes, their mechanism of action, possible interaction with other treatment options, the existing management guidelines and the results of the clinical trials, and the major cardiovascular and renal adverse events. In addition, we have focused on the effects of Sglt-2 inhibitors in heart failure patients. As the literature review requires a careful analysis of the quality and the quantity of research findings, we have tried to gather a wide range of information from the scientific databases to find evidence-based material. For this purpose, a systematic search of the available literature was performed (6). Prior to the literature search keyword selection was performed to include as wide range of articles as possible. The relevant literature has been screened from the very beginning of digitalizing of the articles up to May 2, 2020. The selection of the articles was based on the screening of the article title and the abstract. The search was limited to English results only. After that the databases for the systematic search where selected. The Medline (PubMed) and Embase were chosen as the most relevant, based on the research question and the coverage.

Keywords: SGLT-2 inhibitor, Type-2 diabetes, Heart Failure, Cardiovascular Risk

Sažetak

Naslov: Inhibitori SGLT-2 U liječenju Bolesnika Sa Šećcernom Bolešću Tip 2 I Zatajivanjem Srca

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U ovom smo pregledu literature saželi vrste inhibitora Sglt-2 za liječenje dijabetesa tipa 2, njihov mehanizam djelovanja, moguću interakciju s drugim metodama liječenja, postojeće smjernice za zbrinjavanje te rezultate kliničkih ispitivanja i glavne štetne učinke na kardiovaskularni sustav i bubrege. Osim toga, usredočili smo se na učinke inhibitora Sglt-2 na bolesnike sa zatajenjem srca. Budući da pregled literature zahtijeva pažljivu analizu kvalitete i količinu rezultata istraživanja, pokušali smo prikupiti širok raspon informacija iz znanstvenih baza podataka kako bismo pronašli materijal koji se temelji na dokazima. U tu svrhu izvršeno je sustavno pretraživanje dostupne literature (6). Prije pretraživanja literature izvršen je izbor ključnih riječi kako bi se uključio što širi spektar članaka. Relevantna literatura pregledavana je od samog početka digitalizacije članaka do 2. svibnja 2020. Odabir članaka temeljio se na pregledavanju naslova članka i sažetka. Pretraživanje je bilo ograničeno samo na rezultate na engleskom jeziku. Nakon toga su baze podataka za sustavnu pretragu bile odabrane. Medline (PubMed) i Embase odabrani su kao najrelevantniji, na temelju istraživačkog pitanja i pokrića

Ključne riječi: Inhibitor SGLT-2, Dijabetes tipa 2, Zatajenje srca, Kardiovaskularni rizik

Introduction

Type two diabetes (T2DM) is a condition characterized by insulin resistance, hyperglycemia and disturbances in insulin secretion(1). It is the most common metabolic condition and serves as a basis of significant morbidity and mortality.(2) Hyperglycemia is not only the biochemical marker for the diagnosis of T2DM, but also plays a pivotal role in the development of insulin resistance and pancreatic cells failure, known as glucotoxicity (2). Therefore, improved control of blood glucose in diabetic patients have become one of the keystones of the strategic management, and effectively ameliorates the metabolic abnormalities that contribute to the progressive course of the disease. On the other hand, the T2DM is associated with significant cardiovascular risks, and the international guidelines state the importance to prevent and lower the risk of cardiovascular complications during T2DM treatment (3,4). There are many discrepancies concerning the impact of glucose lowering on cardiovascular outcomes coming from the international glycemic control trials. As the cardiovascular disease in diabetes can have multifaceted pathogenesis, it would beneficial to have a compound that attenuates the risk in multiple directions, which is beyond the glycemic control alone. Till now, the specific cardiovascular effects of the main glucose lowering drugs, such as glinides, sulphonyl urea, metformin, thiazolidinediones, insulin, glucagon-like peptide-1 receptor analogues or dipeptidyl-peptidase-4 (DPP-4) inhibitors have not been elucidated (5). From this perspective the Sodium glucose cotransporter-2 (SGLT-2) inhibitors, which represent a new class of glucose lowering drugs, and act by reducing the renal glucose reabsorption, are under investigation in international double blinded randomized controlled trials, to assess the effectiveness, feasibility and long-term outcomes for the diabetic patients. Some of them are already available in the market. To

understand the effects of SGLT-2 inhibitors in diabetic patients, a literature review has been performed with special emphasis on patients who have increased risk of cardiovascular events AND/OR heart failure. In addition, we provide the characteristics of different types of SGLT-2 inhibitors, their mechanism of action, and known adverse effects.

Interaction between T2DM and Heart Failure

The prevalence of heart failure increases globally and affects at least 26 million people worldwide (7). The heart failure society of America constantly updates the ACC/AHA/HFSA heart failure guideline, which highlights the multidisciplinary approach to improve the clinical outcome of this condition. Although, T2DM and heart failure are each connected with significant mortality, they often share the same pathophysiological chains and need integrated management guidelines. Rubler et al. first introduced the term "diabetic cardiomyopathy" to describe the changes of the heart tissue due to diabetes mellitus. Observational studies have shown that the patients having T2DM demonstrate 2 to 4-fold increased risk of heart failure development. T2DM is an important risk factor for the development of asymptomatic ventricular dysfunction (8). It is the presence of diastolic or systolic dysfunction in a patient with diabetes in case when there are no other obvious causes for cardiomyopathy. The pathophysiology, how hyperglycemia can lead to heart failure is summarized in Figure 1(9).

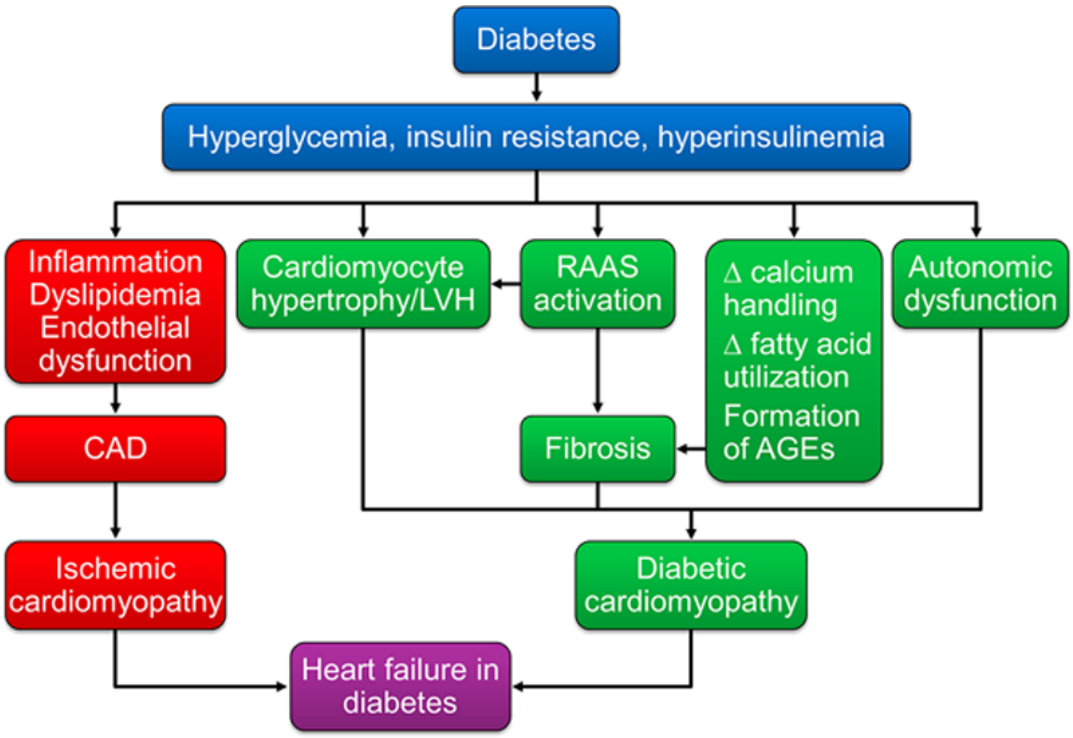

Figure 2. The T2DM factors trigger a cascade of events, that contribute to the development of heart failure.

The advanced glycation end products cause cross-links in collagen molecules, which leads to accumulation of fibrose tissue with increased myocardial stiffness and impaired cardiac relaxation. Furthermore, hyperglycemia leads to the activation of the local renin–angiotensin–aldosterone system (RAAS). The overproduction of angiotensin II and aldosterone exacerbates cardiac hypertrophy and fibrosis and leads to diastolic dysfunction(10). It is worth to mention the hemoglobin A1c fraction can serve as a predictive marker for the heart failure development. Each 1% increase in hemoglobin A1c (HbA1c) increase leads to 8% to 36% increment of the heart failure development. The ARIC (Atherosclerosis Risk in Communities) trial revealed a progressively increasing risk of incident heart failure hospitalization with a rising HbA1c (11). In addition, recent data from the clinical trials underscored that heart failure is one of the critical outcomes of T2DM, and the suggestion is that glucose lowering agents can influence the risk of

heart failure development. (9) From this perspective *Sglt-2 inhibitors* serve as a good choice for the clinician, as they provide modest glycemic control and can be used in patients with heart failure.

The mechanism of action of Sglt-2 inhibitors based on literature data.

Recent investigations have proposed the inhibitors of the renal sodium-glucose cotransporter as a new therapeutic agent for the treatment of the type two diabetes. These antidiabetic agents, known as the Sglt-2 inhibitors, have the potential to improve glycemic control while avoiding hypoglycemia. In addition, they can promote the weight loss. In this section we will summarize the available data concerning efficacy, the mechanism of action, and the safety of the Sglt-2 inhibitors.

Two distinct types of glucose transporters exist in our organism, the GLUT transporters, which work mainly based on chemical gradient, and the SGLT transporters, which require energy for the glucose cotransport (12). Two types of sodium-glucose cotransporters have been described, SGLT1 and SGLT-2, and the homology between SGLT1 and SGLT-2 is approximately 58% (13). Their characteristics and typical location in the renal system can by found in Table 1 and Figure 1 respectively.

Table 1. The location and biochemical characteristics of the SGLT1 and SGLT-2 transporters in renal system

	SGLT1	**SGLT-2**
Renal location	S3 segment of proximal tubule	S1 segment of proximal tubule
Sugar selectivity	Glucose = galactose	Glucose >g galactose
Na/glucose stoichiometry	1:2	1:1
Glucose affinity	High (0.4 mm)	Low (2 mm)

Glucose transport capacity	Low (2 nmol/mg · min)	High (10 nmol/mg · min)
Clinical syndrome resulting from mutation	Diarrhea	Glucosuria
Source [7]		

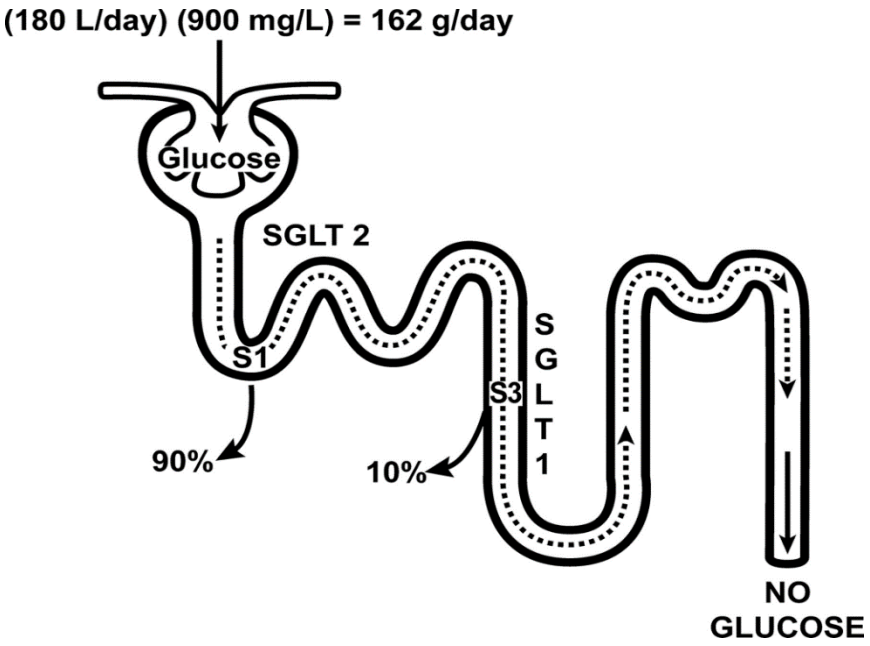

Figure 2. Renal tubular mechanism of glucose reabsorption(2).

In diabetic patients, the hyperglycemia results in an increased filtered glucose load in renal system and as a consequence, the glucose reabsorption via proximal renal tubular cells, increases. This becomes possible due to the increase in SGLT-2 gene expression, reported in experimental studies (14). SGLT-2 inhibitors block the activity of the SGLT-2 channels in the proximal tubule, thus promoting the renal excretion of glucose. In addition, although, the currently available SGLT-2 inhibitors almost completely block proximal tubular glucose

reabsorption, the urine glucose excretion studies show, that the measured inhibition is less than 50 percent.

Types of SGLT-2 Inhibitors, is there a class effect

Regardless of the type, the available SGLT-2 inhibitors share similar pharmaco-kinetic characteristics, including rapid oral absorption, and the hepatic metabolism mainly occurs via glucuronidation. The long elimination half-life allows the patients to take the drug on a once-daily basis. There is still lack of evidence about the clinically relevant drug–drug interactions (15). The characteristics of some SGLT-2 inhibitors already available in the market, can be found on Table 2.

Table 2: *Abbreviations:* NA not applicable, $T_{1/2}$(h) elimination half-life, tmax time to maximum (peak) drug concentration. Source (10)

Name	Dapagliflozin	Canagliflozin	Empagliflozin	Ipragliflozin
Oral bioavailability (%)	78	65	>60	NA
Food effect	Not clinically relevant	Not clinically relevant	Not clinically relevant	Not clinically relevant
Tmax (h)	1-2	1-2	1	1-2
Volume of distribution (L)	118	119	74	NA
Plasma protein binding (%	91	98	86	NA
$T_{1/2}$(h)	12.2	11-13	12.4	10-13
Metabolism	Extensive glucuronidation to inactive conjugates(primarily dapagliflozin3-Oglucuronide)	Extensively metabolised by O-glucuronidation to two major inactive metabolites (M5 and M7	Extensively metabolised by glucuronidation and, to a lesser extent, oxidation to 6inactive metabolites	Extensively metabolized by glucuronidation to two major inactive metabolites (M2 and M4)
Elimination	Primarily in urines as	Elimination in urines and	Eliminated in urine and faeces:	Primarily in urine as inactive

	inactive metabolites:2 % eliminated as unchanged drug in urine	faeces:1 % eliminated as unchanged drug in urine	28.6 % excreted unchanged in urine	metabolites: B1 % eliminated as unchanged drug in urine
Drug interactions	Not clinically relevant	Not clinically relevant	Not clinically relevant	Not clinically relevant

Glycemic efficacy of different types of SGLT-2 inhibitors

When compared to other glucose lowering agents the SGLT-2 inhibitors are relatively weak, with mean reductions in glycated hemoglobin (A1C) compared with placebo ranging between 0.4 to 1.1.

The meta-analyses of clinical trials, which compared SGLT-2- inhibitors with placebo or active comparators, including metformin, sulfonylurea, etc., SGLT-2 inhibitors reduced A1C by approximately 0.5 to 0.7 percentage in comparison with placebo and the mean difference versus active comparators was -0.06 to -0.13 percent (16).

The results of the trials

The double-blind trial, 814 patients with type 2 diabetes administered were randomly assigned to dapagliflozin or glipizide. Previously they were treated with metformin. The mean reduction in A1C was similar in both groups. In addition, Dapagliflozin reduced weight and the hypoglycemia episodes were fewer in comparison with glipizide severe (0 versus 0.7 percent with glipizide) (17).

Another trial compared the effects of dapagliflozin (2.5, 5, or 10 mg once daily) in inadequately controlled 808 patients with type 2 diabetes with placebo. in a 24 weeks period, A1C decreased by 0.79 to 0.96 percentage points in case of dapagliflozin compared with 0.39 percentage points with placebo. As previously, Dapagliflozin reduced weight as compared with placebo. Interestingly, the rate of hypoglycemic episodes was lower in placebo group (56.6 versus 51.8 percent) (18).

The mean reduction in A1C from baseline was significantly better in a 52-week, double-blind trial with canagliflozin than sitagliptin, where patients received canagliflozin (300 mg daily) or sitagliptin (100 mg daily). Canagliflozin reduced weight and systolic blood pressure in comparison with sitagliptin. The overall incidence of adverse events was not differed significantly between the groups (19).

In a 52-week, double-blind trial, where 1452 patients with type 2 diabetes, having inadequate control for the A1C levels, and were assigned to glimepiride or canagliflozin, showed similar results, when compared the1C from baseline was similar in the glimepiride and lower-dose canagliflozin groups' A1C levels. The proportion of patients achieving an A1C <7 or <6.5 percent was not differed significantly between the groups (approximately 56 and 31 percent of patients, respectively). In addition, Canagliflozin treatment was associated with less frequent severe hypoglycemia (<1 compared with 3 percent) but with more frequent genital yeast infections(20).

The 52-week trial, where patients with type 2 diabetes assigned to empagliflozin (10 or 25 mg once daily) or placebo, revealed significantly efficient reduction in A1C levels. Compared with

placebo, empagliflozin effectively reduced insulin doses by 9 to 11 units per day and weight by 2.4 kg as well (21).

In another trial, the SGLT-2 inhibitor Ertugliflozin reduced weight and was associated with less frequent severe hypoglycemia (<0.2 compared with 2.3 percent) but with more frequent genital yeast infections in comparison with glimepiride.

Taken together, these results highlight the ability of the SGLT-2 inhibitors to control the glucose levels, and can lead to weight loss and decrease systolic blood pressure.

Possible Mechanisms Responsible for SGLT-2 Inhibitor effects on cardiovascular and renal outcomes.

Till now, the effects of the SGLT-2 inhibitors on cardiovascular system were carried out in a very high-risk population. And there are few data about the possible effects in lower risk patients. The clinical trials designed in this way, aimed to increase the hazard rate for major cardiovascular disease and complete the experiments in a relatively brief period.

In one of the trials, which was specifically designed specifically to evaluate cardiovascular morbidity and mortality, 7028 patients with type 2 diabetes and having heart failure were randomly assigned to empagliflozin. The vast majority of patients were taking antihypertensive and lipid-lowering agents to correct the blood pressure, and cholesterol, respectively. Part of patients (48%) in each group were taking insulin as well. The primary outcome of this trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. This parameter occurred in fewer patients assigned to empagliflozin than to placebo after three years follow up, and there was a significant reduction in estimated risk of death from

cardiovascular causes (3.7 versus 5.9 percent with placebo; HR 0.62, 95% CI 0.49-0.77). In addition, the hospitalization rate for heart failure was lower as lower in the empagliflozin group, and the patients had reductions in weight, systolic and diastolic blood pressure, which was not accompanied by the increase in heart rate. (22)

Another trial assessed the canagliflozin effects on cardiovascular, renal, and safety outcomes in patients with type 2 diabetes and high cardiovascular risk. The mean follow-up period was 3.6 years. The primary outcome and the hospitalization for heart failure as previously, occurred in fewer patients in the canagliflozin group in comparison with placebo.

Microvascular effects of SGLT-2 inhibitors

In the empagliflozin trial described above, researchers have evaluated the microvascular effects of the substance as a secondary outcome. These included retinal photocoagulation, vitreous hemorrhage and diabetes-related blindness. The occurrence of the vascular effects was much less pronounced in the empagliflozin group as compared with placebo. The worsening nephropathy parameters, defined as progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease were measured as well. Although there were significant reductions in each component, the death ratio from the renal disease was the same in both groups. From the perspective, that the study was performed in a relatively brief period and the glucose lowering effects of empagliflozin are modest, the microvascular effects of the empagliflozin are not likely to be driven by its glucose lowering property, and open a new avenue for future investigations.

Renal effects

In the canagliflozin trial(23), when the researchers assessed the renal outcomes of the substance usage in the patients, who had high cardiovascular risk, the progression of albuminuria (a secondary endpoint) occurred less frequently in the canagliflozin group versus placebo. The renal replacement need surgery or death from the renal causes was occurred less frequently in the canagliflozin group (5.5 versus 9.0 patients per 1000 patient-years, HR 0.60). In contradiction with this, in patients taking canagliflozin or dapagliflozin there have been reports of acute kidney injury and some of the cases required hospitalization and dialysis. The incidence occurred within one month of initiating the drug in approximately one-half cases according to FDA. At this moment, it is still unclear, whether these patients had preexisting chronic kidney disease. On the other hand, in an analysis of the SGLT-2 inhibitor users and nonusers the risk of acute kidney injury was not differed significantly between the groups(24). In any case, it is advisable to assess the renal function prior to initiation of SGLT-2 inhibitors. They should be used with caution in conjunction with other medications that predispose to acute renal injury.

Adverse events

The adverse effects include:

- vulvovaginal candidiasis

The clinical trials have shown, that the administrations of SGLT-2 inhibitors increased incidence of vulvovaginal candidiasis two- to fourfold, seen in 10 to 15 percent of women (25). There is also accumulated evidence, that SGLT-2 inhibitors increase the incidence of urinary tract

infections (8.8 versus 6.1 percent) (26). Recently, the US FDA received reports of potentially fatal urosepsis and pyelonephritis requiring hospitalization. The data concerning the cases of bladder cancers diagnosed among dapagliflozin users remains unclear. However, these findings have prompted the FDA to recommend post marketing surveillance studies, as there is no long term safety data in that regard (27).

- Hypotension

The effects of the SGLT-2 inhibitors, such as osmotic diuresis and intravascular volume contraction can cause symptomatic hypotension. This is especially important in older patients, who take diuretics or angiotensin receptor blockers (28).

- Acute kidney injury

(See the renal effects section)

- Bone fracture

It is likely, that SGLT-2 inhibitors reduce bone mass and increase bone fractures. In a two-year, placebo-controlled trial, patients in the canagliflozin compared with control group had progressively greater loss of bone density over time at the total hip (placebo-corrected declines of 0.9 and 1.2 percent for canagliflozin 100 and 300 mg, respectively) and spine (placebo-corrected declines of 0.3 and 0.7 percent, respectively). Bone fractures occurred more frequently in patients taking canagliflozin (1.4 and 1.5 bone fractures per 100 patient-years exposure to canagliflozin 100 mg and 300 mg, respectively, compared with 1.1 per 100 patient-years in the comparator group (29). The occurrence of low trauma fractures in older individuals after only 12

weeks of therapy, may be due to orthostatic hypotension resulting in postural dizziness and falls. On the other hand, a meta-analysis of trials evaluating safety outcomes did not shown an increased risk of fracture with dapagliflozin or empagliflozin (30).

- Increased risk of amputations

Patients, who are at risk for foot amputation, including neuropathy, foot deformity, vascular disease, and history of previous foot ulceration, should not be prescribed Canagliflozin. Two randomized trials, which assessed the amputation risk in patients with T2DM and established cardiovascular risk, have shown an increased risk of lower limb amputations in patients, taking canagliflozin (amputation incidence 5.9 and 2.8 per 1000 patient-years for patients taking canagliflozin and placebo, respectively) (31). The highest risk was observed in patients with a history of prior amputation, peripheral vascular disease or neuropathy.

- Diabetic ketoacidosis

In the patients taking SGLT-2 inhibitors, the absence of the substantial hypoglycemia can delay the recognition of the possible "euglycemic" diabetic ketoacidosis, recently reported in a variety of cases(32). In case, if the patient has nausea, vomiting, or malaise, serum ketones should be measured, and the SGLT-2 inhibitors should be discontinued if acidosis is confirmed.

Contraindications and possible interactions with other drugs

The SGLT-2 inhibitors should be avoided, when there is ketosis-prone type two, of type one diabetes, and when the glomerular filtration rate is less than 60 mL/min. The medications, that can increase the risk of acute renal injury, should be used with caution in conjunction with

SGLT-2 inhibitors. These include angiotensin-converting enzyme AND/OR inhibitors/angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs, diuretics. In those with low mineral density, the SGLT-2 inhibitors should be avoided.

There is still uncertainty about the management of the patients with heart failure, as on the one hand this comorbidity can predispose to acute renal injury and on the other hand the SGLT-2 inhibitors have a positive effect on cardiovascular system when taken systematically.

Clinical perspectives and prescription guidelines for SGLT-2 inhibitors in heart failure

Patients with T2DM do not need SGLT-2 inhibitors as the first line therapy, given their modest improvement in glycemia, cost, lack of long-term safety data on the effects of prolonged glucosuria. Patients should start with diet, weight loss and metformin. The summary of glucose lowering agents can be found on Table 3.

Table 3: Antihyperglycemic pharmacotherapy

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			

Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated			
TZDs	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5[a]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, expensive
Source (33)			

From the clinical perspective, the SGLT-2 inhibitors can be usable when:

● The patient with cardiovascular disease cannot reach to the normal glycemic values when using metformin or lifestyle modifications. In this case, Empagliflozin is the preferred choice for the clinician.

● The SGLT-2 inhibitors can serve as a third-line agent in patients with inadequate glycemic control, when for some reason combination of metformin and insulin is not a therapeutic option.

● The SGLT-2 inhibitors can serve as a third-line agent in patients with uncontrolled glucose values, who take the combination metformin and insulin therapy, and in whom glucagon-like peptide-1 (GLP-1) receptor agonists are contraindicated.

● As a second agent, when the patients, who are unwilling or unable to consider injection therapy and in whom weight gain is a significant issue.

When the decision has already been made, empagliflozin will be a choice of therapy, when there is a prior history of the myocardial infarction. Canagliflozin is another choice, although there is an increased risk of lower limb amputations and fractures in canagliflozin-treated patients. The benefits and risks' information in patients who have not had a major CVD event are still not sufficient and leave a way for future investigations. As there are no significant differences with regard to A1C lowering, weight reduction, or risk for mycotic infections, the choice of agent is often dictated by cost and insurer preference.

The pretreatment evaluation includes:

- Assessment of the volume status and renal function (the hypovolemia should be corrected prior to the initiation of the treatment).

- Bone density evaluation
- Liver function assessment in case of canagliflozin or dapagliflozin.

When there is an increased risk of hypoglycemia, dose reduction strategies should be implemented to avoid dose-dependent effects.

Monitoring

Besides glycemic indices, some other parameters should be closely monitored, in case if the SGLT 2 inhibitors are prescribed. These include:

- Renal function

The serum creatinine should be checked after three months from the therapy initiation when the glomerular filtration rate is more than 60ml/min. In case if stable, then annually or as clinically indicated.

When glomerular filtration rate is between 45 and 60 mL/min, then serum creatinine should be measured every three months. This is especially important, when patient takes canagliflozin and empagliflozin.

- Patients, who take insulin or insulin secretagogues, should be monitored for fasting and pre-meal fingerstick glucose for the first few weeks following initiation or dose escalation of SGLT-2 inhibitors. Insulin dosing should be decreased by 10 to 20 percent and insulin secretagogue dosing by 50 percent if blood glucoses <80 mg/dL are measured.
- A1C should be measured at least twice yearly in patients meeting glycemic goals.

Questions to address in future preclinical and clinical research with SGLT-2 inhibitors

There are many uncovered questions to be addressed regarding the pathophysiology, optimal pharmacotherapy, and co-disease management strategies for patients with T2DM and heart failure. Well- designed clinical trials and prospective population-based studies are needed to find the best possible combination of existing drugs. The ongoing studies, which aim to evaluate the therapeutic efficiency of SGLT-2 inhibitors are summarized in Figure 3 (34).

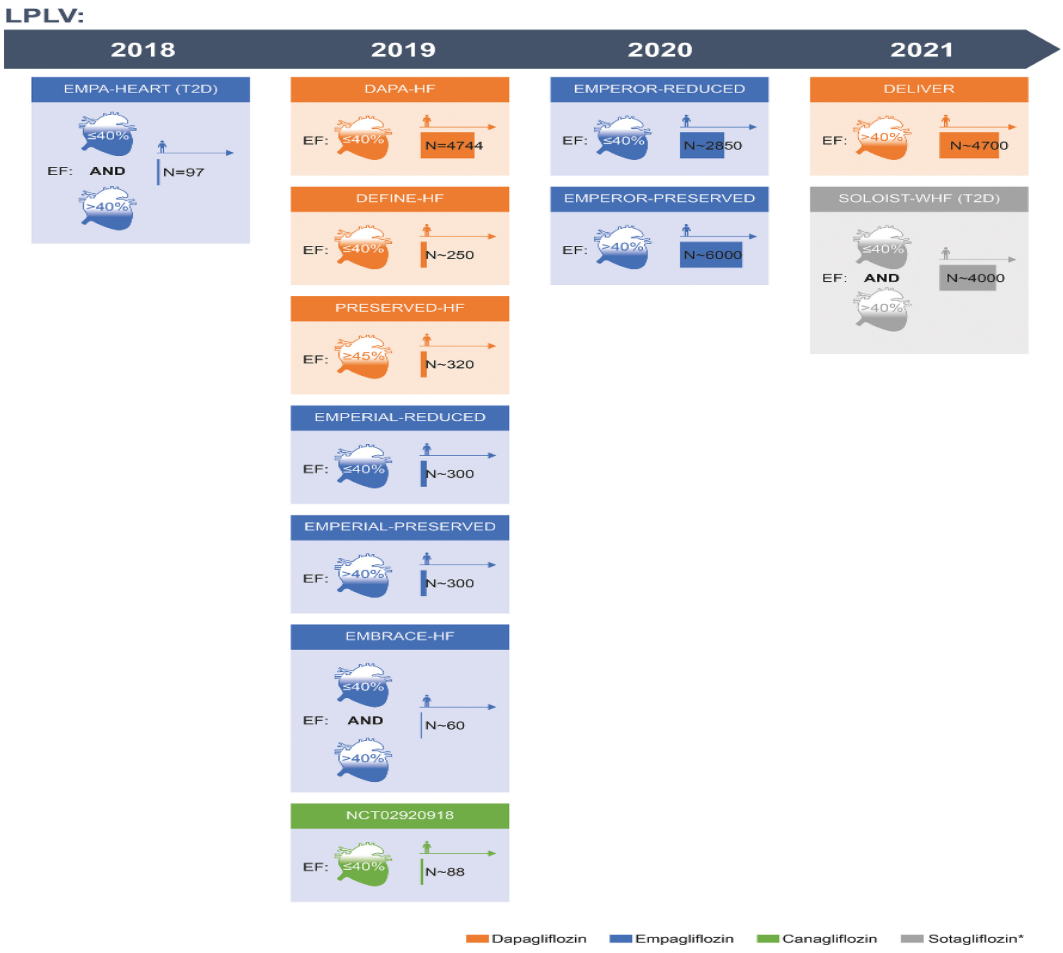

Figure 3

In Figure 3,the larger upcoming dapagliflozin and empagliflozin outcome trials (N>2000) in both HFrEF (DAPA- HF [Dapagliflozin And Prevention of Adverse- outcomes in Heart Failure] and

EMPEROR- Reduced [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction]) and HFpEF (DELIVER [Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure] and EMPEROR- Preserved [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction]), are of particular interest. The intensity of glycemic control via the SGLT-2 inhibitors may need to be tailored to the stage and severity of heart failure, with close monitoring for safety and efficacy of T2DM therapies. In other trials, which were aimed to investigate renal and cardiovascular outcomes with SGLT inhibitors, may shed the light on the extent to which the renal effects of SGLT- 2 inhibitors contribute to the cardiovascular benefits.

In conclusion, the SGLT- 2 inhibitors have the potential to be an effective class of drug for the prevention of heart failure in patients with T2DM. Accumulated evidence indicates that these drugs may promote combined renal and cardiac beneficial effects and hold promise for the treatment of heart failure. Whether this promise translates to clinical efficacy remains to be seen, and the generated data will elucidate the safe use of SGLT-2 inhibitors in patients with heart failure AND/OR renal dysfunction.

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Biography

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