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Review

Impact of SGLT2i on cardiovascular outcomes and heart failure in patients with type 2 diabetes

Juan José Rodríguez†, Luis Ortega-Paz*†, Salvatore Brugaletta and Manel Sabaté

Department of cardiology, cardiovascular institute, hospital clinic, Biomedical Investigation Institute, IDIBAPS, Barcelona, Spain

*** Correspondence:** Email: lgortega@clinic.cat; Tel: +34932279305; Fax: +34932279305.

† These two authors contributed equally.

Abstract: The concurrent management of type 2 diabetes mellitus and heart failure presents several challenges and unmet clinical needs. The sodium-glucose cotransporter 2 inhibitors (SGLT2i) are new generation of oral hypoglycemic agents, they inhibit renal glucose reabsorption and increase renal glucose excretion, thus lowering plasma glucose levels and contributing to a modest reduction in HbA1C. In two pivotal randomized clinical trial, SGLT2i have showed a clinically important reduction in cardiovascular mortality and hospitalization due to heart failure. However, also important adverse effects such as increased risk of bone fractures and lower limb amputations were found. Currently, physiological mechanisms leading to cardiovascular benefits with SGLT2i are not completely understood, but it seems accepted that some of these benefits are related to non-glycemic effects. In this review, we analyze the available clinical evidence focusing in cardiovascular outcomes and heart failure, physiological mechanism of action, and comment on future directions of research.

Keywords: sodium-glucose cotransporter 2 inhibitors; dapagliflozin; canagliflozin; empagliflozin; diabetes mellitus; cardiovascular outcome trials; heart failure

1. Introduction

About 30% of the patients with type 2 diabetes mellitus (T2MD) will develop heart failure [1]. T2DM patients have an increased cardiovascular mortality, heart failure related hospitalization and longer hospital stays when compared to patients without DM [2]. Moreover, the treatment of both

conditions presents several therapeutic challenges. It is well known that previous trials have shown an increased risk of heart failure hospitalizations in patient treated with specific oral antidiabetic drugs [3].

The sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a new type of oral antidiabetic drugs. They inhibit renal glucose reabsorption and increase renal glucose excretion, thus lowering plasma glucose levels. This unique mechanism of SGLT2i action is insulin independent, thus improving glycemic control without promoting hypoglycemia in the absence of exogenously administered insulin [4]. Recently, these drugs have shown important improvement in cardiovascular outcomes in patient with T2DM [5,6].

The objective of this review is to analyze the impact of SGLT2i on cardiovascular outcomes and chronic heart failure in randomized clinical trials, proposed physiological mechanism, and future perspectives.

2. Sodium-glucose cotransporter 2 inhibitors

2.1. Mechanism of action and efficacy

SGLT2 are a member of a sodium-glucose cotransporter family being the major cotransporter involved in glucose reabsorption in the kidney, in the epithelial cells of luminal membranes of S1 and S2 segment in the convoluted tubule. This co-transporter is responsible of the 97% renal glucose reabsorption (Figure 1) [7]. The SGLT2 receptor is not expressed in the myocardial tissue [8].

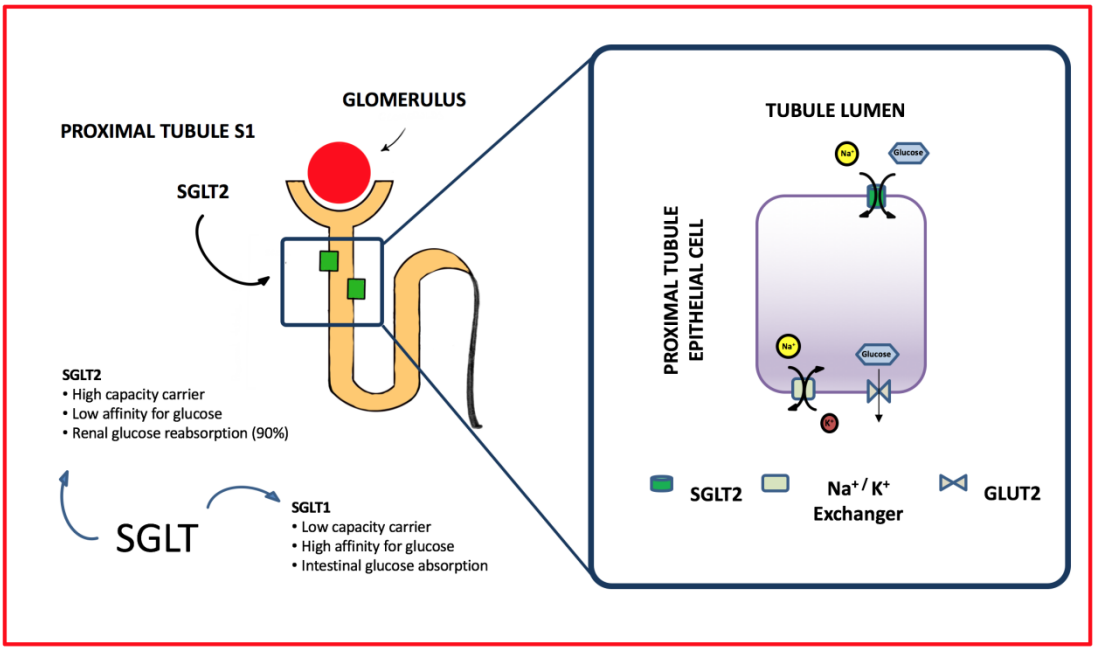

Figure 1. Properties of the STGL2 receptor. SGLT2: sodium-glucose cotransporter 2; GLUT2: Glucose Transporter 2.

Other members of this family are the SGLT1, responsible for the 10% glucose renal reabsorption, being its main role related to intestinal glucose absorption [9].

The SGLT2 inhibition causes a higher rate of glycosuria (40 to 80 g per day) and a decrease of the HbA1c of 0.7% to 0.9%. Osmotic diuresis contributes to a reduction in the extracellular volume decreasing blood pressure by 3 to 5 mmHg. Moreover, the impaired energy balance due to glycosuria results in weight loss (2–3 kg) (Figure 2) [4–6,9].

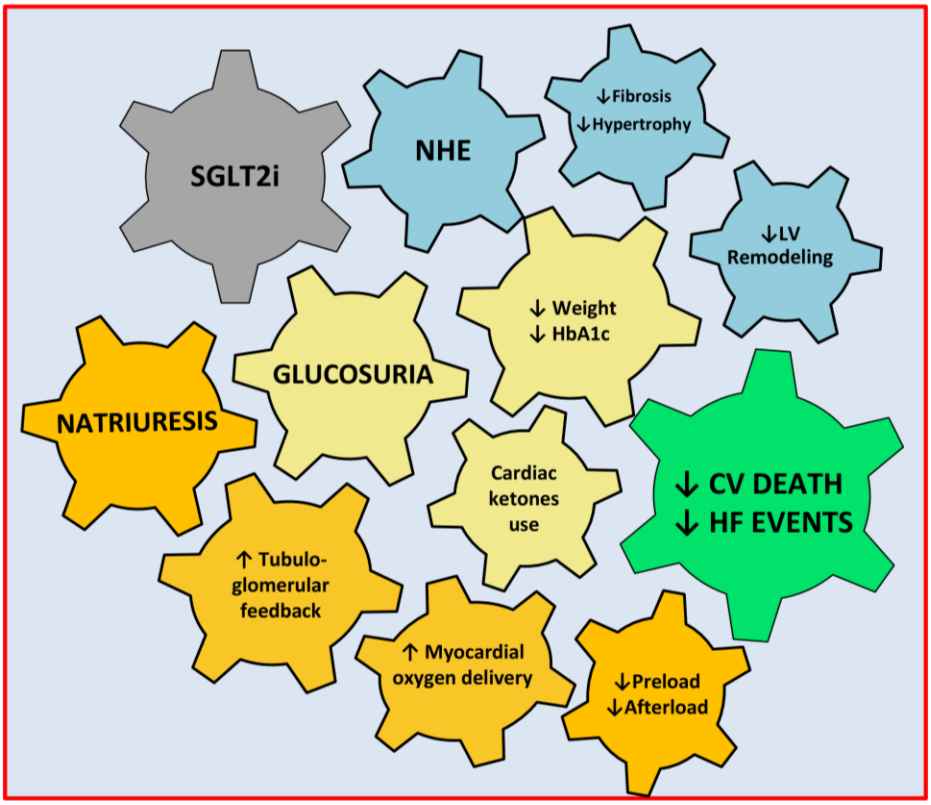

Figure 2. Physiological mechanisms leading to cardiovascular benefits with SGLT2i**.** There are three main mechanism by which SGLT2i can improve clinical outcomes in diabetic patients: Glucosuria, natriuresis, and NHE inhibition. All these pathways interact together to produce the final reduction of cardiovascular death and heart failure events. However, some of these pathways could also be related to the some of the observed adverse effects. SGLT2i: sodium-glucose cotransporter 2 inhibitors; NHE: Sodium Hydrogen Exchanger; LV: Left ventricle; CV: Cardiovacular; HF: Heart failure.

2.2. Adverse effects and security warnings

The most common side effects in patients treated with SGLT2i were related to glycosuria, such as genital and urinary infections. A complete list of adverse events is shown in Table 1.

Regarding dapaglifozin, a high rate of bladder cancer was registered, being considered as a contraindication in patients with such affection [10]. Meanwhile, with canagliflozin, in randomized clinical trials, a higher than expected rate of low trauma fractures and lower limb amputations (predominantly toe and midfoot) were found [6]. Patients with history of prior amputation, peripheral vascular disease, and neuropathy were at highest risk for amputation. Canagliflozin is not recommended in patients with these risk factors. It remains uncertain whether these adverse effects are specific of each drug or could be presented as a class effect.

An increased risk of ketoacidosis has been observed in patients in treatment with SGLT2 inhibitors. Even if glycaemia is in the normal range, if nausea, vomiting or metabolic acidosis appear, patients treated with this type of drugs must be evaluated for ketone bodies in urine and serum. We also have to remember that SGLT2i are not recommended for the treatment of Type 1 diabetes [11].

3. SGLT2i and cardiovascular outcomes

Currently, there are two main randomized clinical trials that compare efficacy and impact on cardiovascular outcomes: EMPA-REG OUTCOME (Empagliflozin) and CANVAS Program (Canagliflozin) (Table 2).

3.1. EMPA-REG outcome

In the EMPA-REG trial, patients in the empagliflozin group presented a lower rate of major adverse cardiovascular events (MACE) when compared to placebo. This decrease was similar when comparing two different treatment doses (10mg vs 25mg) and independent of the glycemic control. A reduction in cardiovascular mortality appeared to be. Of note, the treatment with empagliflozin was not associated with a reduction in ischemic events, such as myocardial infarction (MI) and stroke [5]. Thus, the lower cardiovascular mortality seems to be driven by a reduction in non-ischemic events.

3.2. CANVAS Program

The CANVAS Program integrates data from the CANVAS and CANVAS-R trials [6]. The patients treated with canagliflozin presented a lower rate of MACE when compared to placebo. Eventually, regarding the individual endpoints, there was no difference in the all-cause mortality or in cardiovascular mortality between canagliflozin and placebo. Furthermore, there was no difference in the ischemic events (MI and stroke).

3.3. EMPA-REG vs CANVAS

Both trials were performed according to the FDA regulation of antidiabetics drugs and cardiovascular safety [12]. The objective and design are very similar, although there are some differences that should be mentioned. Regarding the population of the trials, the EMPA-REG trial included patients with history of ischemic events such as: MI, coronary artery disease (CAD), stroke and periphery arterial disease (PAD) [5]. Meanwhile, the CANVAS, performed a different inclusion criteria definition: Patients aged between 30 and 49 years should have a documented symptomatic CAD and patients older than 50 years should have two or more prespecified cardiovascular risk factors with or without documented CAD or previous ischemic events (MI or stroke) [6]. This difference in the selection criteria was related to differences in the baseline characteristics of the patients in both trials. In the EMPA-REG trial a 75.6% suffered CAD (46.7% with a previous MI). However, in the CANVAS Program, patients with CAD only represented a 54.4%.

These differences should be considered when the outcomes of the trials are compared. Despite both trials met their primary composite endpoint, in the EMPA-REG, a reduction in the

cardiovascular mortality existed, whereas not in the CANVAS. Moreover, neither studies had impact on the ischemic events (MI or stroke) (Table 2). It remains uncertain whether these issues could explain the differences in the results or if a real difference exists in the efficacy of the drugs.

3.4. Findings in perspectives

The positive results of these studies have created a great expectation in the cardiology and endocrinology scientific communities. However, the findings need to be kept in perspective. The important cardiovascular benefit of empagliflozin and canagliflozin, while statistically significant and clinically relevant, was observed in high-risk population, with established cardiovascular disease (CVD) at baseline. Specifically, in patients treated with canagliflozin, the increased risk of amputations should be considered. The low impact of the SGLT2i in the glycemic control suggests that extra-glycemic effects were responsible for the CVD outcome. However, it remains unknown if these drugs could cause the same effects on T2DM patients without CVD. Furthermore, the precise mechanism by which reduction in MACE was produced is still not well understood.

4. **SGLT2i and heart failure**

Considering the incremented risk of heart failure with counted oral hypoglycemic agents, the regulatory agencies focus special attention on heart failure outcomes [3–6,9–12]. In both EMPA-REG and CANVAS, the impact of SGLT2i on heart failure, defined as hospitalization due to these event, was analyzed (Table 2).

Despite the evidence between glycemic control and microvascular events, no trials have demonstrated the relation between glucose levels in blood stream and heart failure.

4.1. EMPA-REG outcome

In the EMPA-REG trial an impressive reduction in the hospitalization due to heart failure was found (NNT: 74.1). Moreover, in the empagliflozin group there was a reduction of the investigator-reported incidence of heart failure (NNT: 58.8) and introduction of loop diuretic treatment (NNT: 21.7). This decrease was observed in both, patients with and without heart failure, and was consistent in both empagliflozin doses. These data suggest a reduction in the incidence and progression of heart failure [5,6,9–13]. Only 10% of the included patients suffered a previous cardiac failure event, based on the narrow standard MedDRA query ‘cardiac failure’ [14]. It should be highlighted that the decrease in cardiovascular deaths was not associated to ischemic events but with a reduction in heart failure events.

4.2. CANVAS Program

In the CANVAS, the canagliflozin group showed an important reduction in hospitalization due to heart failure (NNT: 31.3). There was trend towards a reduction in both, patients with and without heart failure. Patients with heart failure history represent an 11.9% of the sample [6].

4.3. EMPA-REG vs CANVAS

Both trials showed consistent and clinical important reduction on heart failure events. At present, there is more detailed information of the EMPA-REG trial regarding heart failure events, meanwhile post-hoc analysis of the CANVAS is still missing [13–15].

4.4. Findings in perspective

Given the previous unsatisfactory heart failure outcomes with thiazolidinediones and DPP-IV inhibitors, the safety profile of oral hypoglycemic agents have been under scrutiny and several trials have been published regarding the cardiovascular safety of oral hypoglycemic agents [16,17]. Incretin mimetics have also been evaluated [18–20], one of the most recent published studies, the exenatide study of cardiovascular event lowering trial (EXSCEL) [21], evaluated the CV safety of exenatide, added to usual care in patient with type 2 diabetes, demonstrating that it was noninferior to placebo with regarding safety.

Thus, the impressive results of the EMPA-REG and CANVAS are more than welcome. Eventually, there are several issues in relation to the design of these trials. First, none of these trials were sample powered for heart failure endpoints. Second, the selection criteria in both trials were not as strict as in a conventional heart failure trial. In the EMPAG-REG were based on a questionnaire and in the CANVAS on medical history. Third, baseline or follow-up left-ventricular ejection fraction (LVEF) assessment was not performed regularly. Fourth, in both trials approximately only a 10% of the enrolled patients had previous history of heart failure. Fifth, in the subgroup analysis, no benefit in patients taking aldosterone receptor blockers appeared, not knowing if an overlap in the mechanism of these two treatments exists [5,6]. Finally, the proportion of patients with preserved or reduced heart failure remains unknown. Considering all these reasons, despite of an important clinical benefit, further research is needed to completely understand the mechanism and to define which population could benefit more from these drugs.

5. Physiological mechanism of SGLT2i

The beneficial outcomes of SLGT2i related to decrease in progression of heart failure have not been related to glycemic control [22–24]. Several of these mechanisms are still not completely understood and it remains unknown if they can be defined as class effects or specific for each SLGT2i drugs [25].

Some of the proposed mechanisms related to beneficial (✓) and adverse effects (✕) are the following (Figure 2):

5.1. Glucosuria

- ✓ Reduction in the HbA1C
- ✓ Uricosuria and reduction in uric acid
- ✓ Decrease of insulin and increased in glucagon production. Energy substrate change by use of ketones by the heart
- ✓ Reduction in body weight
- ✕ Possible risk of diabetic ketoacidosis
- ✕ Hypoglycemia, specially when combined with insulin or sulphonylureas

✕ Genitourinary infections

5.2. Natriuresis

✓ Increase of tubuloglomerular feedback: Maintenance of euvolemic and reduction of proteinuria
✓ Decrease of renal cortical ischemia, increase in the erythropoietin and hematocrit and therefore an increase in myocardial oxygen delivery
✓ Decrease in arterial stiffness
✓ Decrease in plasma volume: in preload y afterload
✕ Hypotension: Acute kidney injury, falls, fracture, tissue hypoperfusion
✕ Hyperviscosity: Tissues ischemia and risk of lower limbs amputation

5.3. Inhibition of sodium hydrogen exchangers (NHE)

✓ Reduction in LV hypertrophy
✓ Reduction in LV fibrosis and remodeling
✓ Reduction in high-sensitivity troponin I and N-terminal pro-B-type natriuretic peptide

5.4. Direct cardiac effects

Recently, it has been proposed that the direct cardiac effects of the SGLT2i can be related to their interaction with sodium-hydrogen exchangers (NHE). It has been demonstrated that NHE exhibits an increased function in patients with heart failure [26,27]. A higher intracellular calcium concentration, secondary to an increased intracellular sodium, has been related to myocyte injury and hypertrophy, leading to a higher rate of fibrosis, cardiac hypertrophy and heart failure [24].

6. Future perspective

The positive results of the EMPA-REG and CANVAS, specially the reduction in heart failure events, have led to an extensive basic and clinical research. Currently, several randomized clinical trials with the objective to evaluate the impact of SGLT2i in heart failure in diabetic patients, are ongoing (Table 3). These trials were specifically designed with this aim, considering sample size, primary endpoint, cardiac imaging assessment, heart failure specific treatment such as cardiac resynchronization therapy, etc. Eventually, EMPEROR trials will assess both types of heart failure, preserved and reduced. The DECLARE-TIMI58 primary endpoint should be presented in 2019 adding an extensive and high-quality evidence of the cardiovascular safety of SGLT2i. Finally, small trials are evaluating the hypothesis of the possible application of SGLT2i to non-diabetic patients, but probably there is still a long way to go before this could be applied to clinical practice [28,29].

Table 1. Overview of the pharmacological and clinical profiles of different SGLT2i [5,6,30].

	Canagliflozin	**Dapagliflozin**	**Empagliflozin**
Presentation	100 or 300 mg pills once a day	5 or 10 mg pills twice a day	10 or 25 mg pills once a day
Pharmacology	Selective and reversible inhibition of sodium-glucose cotransporter type 2		
	Cmax: 1.0–2.0 hr	Cmax: 2.0 hr	Cmax: 1.5 hr
	Protein bound 99%	Protein bound 91%	Protein bound 86%
	Elimination pathway is glucuronidation, with little involvement of cytochromes		
	Excretion: 33% urine: 41% feces	Excretion: 75% urine: 21% feces	Excretion: 54% Urine: 41% feces
	Half-life: 10.6 hr	Half-life: 12.9 hr	Half-life: 12.4 hr
Glycemic effects	100 mg: −0,91 (−1,09; −0,73)	5 mg: −0,35 (−0,52; −0,18)	10 mg: –0,74 (–0,90; –0,57)
(Δ in HbA1C %)	300 mg: −1,16 (−1,34; −0,98)	10 mg: −0,29 (−0,45; −0,12)	25 mg: –0,85 (–1,01; –0,69)
Indications	In monotherapy when metformin is not considered appropriate.		
	In combination with other hypoglycemic agents, including insulin, in patients not adequately controlled on metformin and these drugs.		
Adverse effects	Renal impairment, back pain vulvovaginal candidiasis, urinary tract infections upper respiratory tract infections, and pharyngitis	Renal impairment, Back pain vulvovaginal candidiasis, urinary tract infections upper respiratory tract infections, and pharyngitis	Nasopharyngitis, urinary infection and hypoglycaemia.
	Increased risk: - lower limb amputation - bone fracture - anaphylaxis and angioedema - Hyperkalemia		
Contraindications	Severe renal impairment*, end-stage renal disease, or patients on dialysis		
Interactions	Other hypoglycemic drugs, diuretics, ARAII or ACEI, Aldosterone inhibitors.	Other hypoglycemic drugs and diuretics	Other hypoglycemic drugs and diuretics
Type 1 Diabetes	No		

*Estimated glomerular filtration rate < 30 mL/min/1.73 m^2. Hr: Hours.

Table 2. Comparison of major SGLT2i cardiovascular outcome randomized clinical trials.

	EMPA-REG OUTCOME (NCT01131676)[5]	**CANVAS PROGRAM (NCT01032629, NCT01989754)**[6]	**DECLARE-TIMI58 (NCT01730534)**[31]
Objective	Asses safety of empagliflozin	Asses safety of canagliflozin	Asses safety of dapagliflozin
Population	Patients with Type 2 Diabetes Mellitus and cardiovascular disease.	Patients with Type 2 Diabetes Mellitus and high cardiovascular risk.	Patients with Type 2 Diabetes Mellitus, Non-Insulin dependent and high cardiovascular risk.
Design	Randomized, parallel assignment, double blinded, placebo controlled.	Randomized, parallel assignment, quadruple blinded, placebo controlled.	Randomized, parallel assignment, quadruple blinded, placebo controlled.
Primary endpoint	MACE* at 4.6 yr	MACE* at 3.6 yr	MACE* up to 6 yr
Enrollment (patients)	7064	10142	17276
Cardiac mortality	Placebo: 5.9% vs. empagliflozin: 3.7% 0.62 (0.49–0.77)	Placebo: 12.8% vs. canagliflozin: 11.6% 0.87 (0.72–1.06)	-
Ischemic events			
Myocardial infarction	Placebo: 5.4% vs. empagliflozin: 3.5% 0.87 (0.70–1.09)	Placebo: 12.6% vs. canagliflozin: 11.2% 0.89 (0.73–1.09)	-
Stroke	Placebo: 3% vs. empagliflozin: 4.8% 1.18 (0.89–1.56)	Placebo: 9.6% vs. canagliflozin: 7.9% 0.87 (0.69–1.09)	
Heart failure			
Hospitalization	Placebo: 4.1% vs. empagliflozin: 2.7% 0.65 (0.50–0.85)	Placebo: 8.7% vs. canagliflozin: 5.5% 0.67 (0.52–0.87)	-
Investigator-reported incidence	Placebo: 6.1% vs. empagliflozin: 4.4% 0.70 (0.55–0.86)	-	-
Introduction of loop diuretic treatment	Placebo: 13.3% vs. empagliflozin: 8.6% 0.62 (0.53–0.73)		

*MACE: cardiovascular Death (Including Fatal Stroke and Fatal Myocardial infarction), Non-fatal Myocardial infarction (Excluding Silent Myocardial infarction), and Non-fatal Stroke. Yr: years.

Table 3. Ongoing randomized clinical trials of the role of SGLT2i on treatment of heart failure

	Population	Design	Endpoint	Comment
EMPEROR-Reduced[32] (NCT03057977)	Chronic HF HFrEF (<40%) ~2850	Randomized Empagliflozin 10mg vs. placebo Parallel Double masking	CV death or hospitalization for Heart Failure at 38 months of follow-up	On top of OMT, including ICD and CRT. Inclusion: EF will be match with NT-proBNP.
EMPEROR-Preserved[33] (NCT03057951)	Chronic HF HFpEF (Preserved or >40%) ~4126	Randomized Empagliflozin 10mg vs. placebo Parallel Double masking	CV death or hospitalization for Heart Failure at 38 months of follow-up	On top of OMT. Structural heart disease within 6-month prior inclusion.
Dapa-HF[34] (NCT03036124)	Chronic HF HFrEF (<40%) and NT-proBNP ≥600 pg/ml ~4500	Randomized Dapagliflozin 5 or 10mg vs. placebo Parallel Double masking	CV death or hospitalization for HF or an urgent HF visit.	On top of OMT, not including CRT.

HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; CV: Cardiovascular; OMT: Optimal medical treatment; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronization therapy; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

7. Conclusions

Due to regulatory agencies' requirements, cardiovascular safety of oral hypoglycemic agents has been extensively studied, but inconsistent results have been previously found. The EMPA-REG outcome and CANVAS Program have not only showed a reduction in major cardiovascular outcomes, but also an improvement in heart failure events. Furthermore, the paradigm of the glycemic control begins to shift to a more clinical outcome related focus. Despite of the important clinical effects of SGLT2i, these results should be taken in perspective, without forgetting the selected and high-risk population included and methodological limitations regarding heart failure outcomes. Additionally, serious adverse events such as increased risk of bone fracture and lower limb amputations, should be considered when prescribing SGLT2i. Further research is needed to determine the mechanism related to benefits and adverse effects of these drugs, and determine their target population in daily clinical practice.

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