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# Sodium-Glucose Cotransporter-2 Inhibitors and Cardiovascular Disease: Lessons and the Future

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**ABSTRACT**

Diabetes mellitus (DM), an epidemic non-communicable disease, is associated with macro- and micro-vascular complications which may result in sudden cardiac death at a young age. Sodium-glucose cotransporter-2 inhibitors (SGLT2-I) emerged as a new therapeutic option for managing DM with cardiovascular complications as well as diabetic patients with multiple risk factors. Three drugs in this class significantly reduced cardiovascular mortality and heart failure events, in both type 2 diabetes mellitus and non-diabetic patients with a reduced ejection fraction, to prevent heart failure related hospitalisation. Evidence of kidney protection was another major advantage provided in more than one study. We reviewed recent SGLT2-I related literature and discuss the benefits beyond the cardiac system.

**Keywords**
Diabetes mellitus (DM); Cardiovascular disease; Sodium-glucose cotransporter-2 inhibitors (SGLT2-I); Renal protection.

## INTRODUCTION

Diabetes mellitus (DM) is a growing problem in developing and developed countries. It is linked to macro-vascular complications such as myocardial infarction, stroke and peripheral artery disease. In addition to micro-vascular complications in the form of retinopathy, nephropathy, neuropathy, or a combination of any of these complications, the inevitable outcome is heart failure (HF). This close association highlighted the need to measure the effect of diabetic medication on the cardiovascular system. For example, biguanides demonstrated a positive effect on the cardiovascular system as well the glucagon-like peptide agonists. Recently three sodium-glucose cotransporter-2 inhibitors (SGLT2-I) had shown a promising outcome.

## DISCUSSION

The pathophysiological cardiac injury due to DM occurs through various mechanisms, with two currently accepted. The first is mediated through atherosclerosis, with DM considered a high-risk for atherosclerotic events resulting in myocardial wall damage.[1] The outcome is heart failure with a reduced ejection fraction. The second is independent of atherosclerosis and mediated by a direct inflammatory effect in the micro-vascular system and myocardium with subsequent fibrosis, also called diabetic cardiomyopathy.[2] Both mechanisms result in HF. Myocardial damage leading to left ventricle (LV) dysfunction and HF is an early and often undetected complication of DM. According to Faden et al[3] two thirds of patients who had DM for more than 5-years, exhibited a variable grade of LV dysfunction.[3] In addition, undiagnosed HF was detected in 28% of patients diagnosed with diabetes during cardiac screening.[4]

Diabetes mellitus can predispose the patient to heart failure with a preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF). In addition to this, the high rate of subclinical heart failure and diastolic dysfunction in diabetic patients contribute to the high rate of heart failure related hospitalization and cardiovascular (CV) death in this population.[5,6] A recent study

in Denmark highlighted the risks DM patients are exposed to, with an incidence of 9% of sudden cardiac death in 14,294 deaths over a 10-year period. It should be noted that the risk of sudden death in the DM group younger than 35-years, was 21.9 per 100,000 person-years compared to 2.6 in the group without DM, and 119.8 *versus* 19.7 in an older age group (36-49-years). The study emphasized the importance of risk factor control, particularly in the younger DM population.[7]

The Swedish Diabetes Register indicated that the decline in the CV death rate in the DM population is slowing.[8] In addition, the decline in major CV related deaths and atherosclerotic events did not correlate with the decline in heart failure or arrhythmia.[9] The 1-year and 3-year all-cause mortality estimates of the Heart Failure Risk Calculator, listed DM as the most important risk stratifier after age and a low ejection fraction in terms of an adverse prognosis.[10] Due to these challenges, the guideline highlights the implementation of an aggressive risk reduction strategy in stage A and stage B of HF-I, the development and the progression of the disease, to prevent HF in diabetes.

Due to the seriousness of these concerns, the unique effect noted with sodium-glucose cotransporter-2 (SGLT2) inhibitors, resulted in the initiation of several SGLT2 inhibitor trials (Table 1). Three trials compared a DM population in terms of primary (multiple risk factors) and secondary prevention (established cardiovascular disease (CVD)). The Empagliflozin Cardiovascular Outcome Event Trail in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) recruited patients requiring secondary prevention, and in the CANagliflozin CardioVascular Assessment Study (CANVAS) program and dapagliflozin effect on cardiovascular events—thrombolysis in myocardial infarction 58 (DECLARE-TIMI 58), 34%-59% of the participants were in the primary arm.[11-13] SGLT2 inhibitors decrease glucose and sodium reabsorption in the proximal tubule as well as nephron hyperfilteration, which enhance urinary glucose and sodiumexcretion.[14] SGLT2-I modulates several factors related to CV risk, including a decreased level of glucose and insulin, sympathetic nervous system activity, blood pressure and arterial stiffness, weight and visceral adiposity, oxidative stress, triglyceride, uric acid, albuminuria and increased High-density lipoprotein (HDL). The DECLARE-TIMI 58 demonstrated that the benefit of SGLT2-I is functional in the primary and secondary prevention categories.[15] The notable conclusion was the improvement observed in the hospitalization for heart failure (HHF) in all three studies: the DECLARE, CANVAS and EMPA-REG. The SGLT2-I demonstrated a benefit in terms of reducing CV death and HHF in patients with HFrEF, the effect that was seen early and continued throughout the trial.[16] In addition, Dapagloflozin for example, resulted in a major adverse cardiovascular events (MACE) relative risk reduction of 16% and an absolute risk reduction of 2.6%, compared to placebo. Though we need 32 patients to prevent one death with ramipril, 56 with simvastatin and 71 with liraglutide, only 39 are required to show a similar effect with empagloflozin.

**Table 1.** *Summary of the Important Differences between the Three SGLT2-I Trials*

| | EMPA-REG OUTCOME[1] | CANVAS Program[2] | DECLARE-TIMI 58[3] |
|---|---|---|---|
| No. of patients | 7000 | 4330 | 17150 |
| Duration of trial (y) | 5 | ≥4 | 6 |
| Age, years, mean (SD) | 63±9 | 63 | 63.9±6.8 |
| Micro-/macro-albuminuria (%) | 40.6 | 30.2 | 30.2 |
| eGFR, mean (mL/min/1.73 $m^2$) | 74.1 | 76.5 | 85.2 |
| % Primary prevention | | 34 | 59 |
| % Secondary prevention | 100 | 66 | 41 |
| 3-point MACE risk | 14 | 14 | 17 |
| CV death | 38 | Neutral | Neutral |
| Non-fatal myocardial infarction | Neutral | Neutral | Neutral |
| Non-fatal stroke | Neutral | Neutral | Neutral |
| HF hospitalization | 35 | 33 | 27 |
| Dose | 10 | 100 | 10 |

Intensive treatment with anti-diabetic agents showed some benefit in terms of atherosclerosis endpoints (myocardial infarction/coronary heart disease (MI/CHD)), but no definite improvement in stroke or mortality.[17] The newer antihyperglycemic agents, however, have shown CV outcome benefits in multiple studies and the CV benefit may be a class effect for SGLT2.[18] The European Society of Cardiology (ESC) guideline provides a strong recommendation for class 1, stating that this group should be added to the treatment of patients with DM with CVD or at very high-risk of CVD.[19] Another class 1 indication for DM patients, was to add SGLT2-I to reduce hospitalization due to heart failure. SGLT2-I is associated with a lower risk in terms of renal end points and recommended if the glomerular filtration rate (GFR) is 30-90 ml/min.[19] In contrast to the renal protective effect observed in the renin-angiotensin-aldosterone system (RAAS) blockade, where the effect is mainly on the afferent constriction, SGLT2-I function through efferent vasodilation. SGLT2-I decrease glomerular pressure, reducing albuminuria.[20] Of interest is that the finding that the Dapagliflozin benefits more than DM patients, as the non-DM group also had a reduced HHF. The benefits surpassed the rare side effects reported, including recurrent genital infection, urinary tract infections and volume depletion. Lower limb amputation, fracture and euglycemic diabetic ketoacidosis, were rarely reported.

## CONCLUSION

In conclusion, SGLT2-I are recommended for the prevention of HF hospitalisation in patients with DM and established CV disease or with multiple risk factors. A significant reduction in CV mortality and HF events was noted in both DM and non-DM patients with a reduced ejection fraction. Research is ongoing to demonstrate a similar effect in patients with a preserve dejection fraction.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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