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" Assessment of cardiovascular outcome in SGLT2- Inhibitors pre-treated diabetic patients with Acute Myocardial Infarction undergoing primary percutaneous coronary intervention (PPCI)"

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ABSTRACT:

Coronary artery disease is strongly linked to chronic conditions like diabetes, increasing the risk of heart failure and major cardiovascular events. SGLT2 inhibitors help control blood sugar in type 2 diabetes patients. Clinical trials show these drugs also significantly improve cardiovascular and renal outcomes in both diabetic and non-diabetic heart failure patients.

The primary aim of this article is to serve as an assessment of the cardiovascular outcomes in diabetic patients who were pre-treated with SGLT2 inhibitors and subsequently underwent primary percutaneous coronary intervention (PPCI) for acute myocardial infarction. Furthermore, the article reviewed the findings of multiple studies and research efforts concerning cardiovascular events, including mortality rates and MACE, as well as the role of SGLT2-I in enhancing outcomes for patients presented with ST-elevation myocardial infarction (STEMI).

In conclusion, compared to conventional treatment approaches; the use of SGLT2-I following myocardial infarction was related with lower rates of all causes of mortality and a reduced incidence of initial hospitalization due to heart failure.

Keywords: SGLT2 inhibitors, primary Percutaneous Coronary Intervention, MACE, acute myocardial infarction (AMI).

NTRODUCTION:

Introduction & mechanism of action:

Sodium-glucose cotransporter 2 inhibitors (SGLT2Is) is considered a novel class of therapeutic agents serves as blood glucose levels reductant. This category features medications as ertugliflozin, empagliflozin, dapagliflozin, sotagliflozin, canagliflozin, which are, in multiple regions, currently accessible. Further, these agents decrease the renal glucose threshold to enhance glycemic control, thereby inhibiting glucose reabsorption in the kidney proximal convoluted tubules and promoting excretion of glucose through urine. Studies have shown that SGLT2Is effectively lower Hemoglobin A1c values, body weight, and blood pressure while keeping cardiovascular status, even used as monotherapy or with other medications. **(Gallo et al., 2015)**

In addition, Empagliflozin has been found to correlate with decrease in body weight and blood pressure status, without affecting heart rate. Moreover, also improves indicators of arterial stiffness, vascular resistance, visceral fat, urinary albumin concentration and plasma uric acid level. Empagliflozin has been also shown to increase levels of both LDL and HDL cholesterol. However, the Most frequent reported adverse effects of Empagliflozin are urinary tract infections and vaginal infections. **(Zinman et al., 2015)**

Although it is the function of SGLT2 and SGLT1 to transport glucose within the cells of the kidney's proximal convoluted tubule (PCT), yet their functions vary. Located in the S1 segment of the PCT; SGLT2 is known as a high-capacity, low-affinity transporter. It is estimated that SGLT2 is Plays a key role in reabsorbing around 90% of glucose, with its expression confined to the kidneys. SGLT2 facilitates glucose uptake into proximal tubule cells against its concentration gradient by using sodium transport. The sodium gradient across the luminal epithelium is kept by ATP-driven sodium extrusion across the anti-luminal membrane into the bloodstream. Intracellular glucose passively diffuses out along a concentration gradient and exits through the anti-luminal membrane into the intercellular space. **(Chao et al., 2010)**

SGLT2-I as a medication for heart failure

The dapagliflozin in heart failure patients (DAPA-HF) study, which started in February 2017, found that dapagliflozin reduced the cardiovascular mortality rates or hospitalization due to heart failure by 26% in patients with heart failure and reduced ejection fraction (HFrEF). As a matter of fact, the reduction was even greater (up to 27%) in non-diabetic patients, which indicate that dapagliflozin can

decrease the risk of major adverse cardiac events (MACEs) regardless of the presence of diabetes. **(McMurray et al., 2019)**

Further, in March 2019, The EMPEROR-Reduced study, in which individual patients with reduced cardiac function than those in the DAPA-HF study are enrolled, showed that compared to control cohort; a reduction of 30% in the cardiovascular death risk or hospitalization for heart failure symptoms, an eight percent drop in risk of cardiovascular mortality and a thirty one percent decrease in heart failure hospitalizations for the first time in the empagliflozin group. (**Packer et al., 2021)**

Heart failure with preserved ejection fraction (HFpEF)

A study named EMPEROR-Preserved study was the first one to encounter its primary endpoint, offering new hope for symptomatic HFpEF patients. Moreover, the DELIVER study was conducted to further explore whether dapagliflozin could achieve similar benefits in HFpEF. This study involved 6,263 HFpEF patients (LVEF >40% with structural heart disease) across NYHA classes II to IV. **(Packer et al., 2021)**

On the other hand, The DECLARE-TIMI58 trial, the multi-center, double-blind, randomized, placebo-controlled study, which had 17,160 with type II diabetes participated, including 1,316 with HFpEF and elevated cardiovascular risk. Over a Follow-up time with a median of four years and two months, dapagliflozin showed significant Advantages in the HFpEF subgroup (LVEF >45%). Similarly, the EMPEROR-Preserved study enrolled 5,988 patients with diastolic heart failure (LVEF >40%) and Follow-up time with a median of of twenty-six months and six days. It was found that Patients treated with empagliflozin had a 21% decreased risk of cardiovascular mortality or hospitalization for heart failure for the first time compared to placebo group. **(Mosenzon et al., 2019)**

In term of Acute decompensated heart failure

A trial called The SOLOIST-WHF trial, which is a multi-center, double-blind, randomized, placebo-controlled study, investigated SGLT2 efficiency in the management of acute decompensation of heart failure patients. The study was conducted on 1,222 participant adults with type II diabetes who were hospitalized for heart failure and managed with diuretic medications, out of which, 79.1% a reduced ejection fraction of left ventricle of less than 50%. The follow-up duration had a median of nine months and six days. Moreover, the overall number of cardiovascular hospitalization reasons and cardiovascular mortality from emergency visits for decompensated heart failure was also the main Finding. With a cardiovascular rate of death of 10.6 percent in the group of sotagliflozin and 12.5 percent in the placebo group, the findings confirmed that the major events risk was reduced by 33% by

sotagliflozin comparable to a placebo. Furthermore, while the placebo group experienced a mortality of 16%, the group of sotagliflozin experienced a mortality of 13%. **(Bhatt et al., 2021)**

Heart failure after acute myocardial infarction

A trial called EMMY trial Examined the consequences of using empagliflozin drug on cardiac function and heart failure biomarkers in patients recovering from acute myocardial infarction (AMI). Prior study had shown a reduction of roughly 50% in NT-proBNP values within six months post-AMI with empagliflozin, prompting this trial to validate those results. A total enrollment of 476 AMI patients, selected based on criteria like creatine kinase levels exceeding 800 U/L, cardiac troponin T/I concentrations >10x the upper normal limit, new ECG signs of myocardial ischemia, imaging-confirmed ventricular wall motion irregularities, or clinically significant ischemic symptoms. The trial remains active, with a 26-week follow-up period underway. Despite SGLT2 inhibitors (SGLT2I) being incorporated into some countries guidelines, their application post-AMI remains cautious. **(Tripolt et al., 2020)**

Current evidence remains limited on the safety and efficacy of medication group called SGLT2I in the heart failure condition after AMI, however, such knowledge gap is aimed to be addressed in the EMMY trial. It was shown that using Rats free of diabetes with post-infarction left ventricular failure, empagliflozin elevated the ejection fraction in both treatment groups, treated early and late, relative to control group. Additionally, the drug enhanced cardiometabolic efficiency and myocardial ATP production. These outcomes imply that SGLT2I could emerge as a viable therapeutic strategy for post-AMI heart failure. **(Butler et al., 2024)**

There are a number of possible mechanisms to adhere to when using SGLT2 inhibitors in treating heart failure. One of the key mechanisms include reducing anteroposterior load. For instance, few of the mechanisms include, enhanced the use of endogenous ketone bodies and metabolism of myocardium energy, Prevention of sodium-hydrogen exchange (which raises the calcium level in mitochondrium, reduction in accumulation of epicardial fat, prevention of myocardium fibrosis and oxidative stress, and Regulation of lipid profile and uric acid. **(Lopaschuk et al., 2020)**

The fresh clinical evidence has helped pushing SGLT2I beyond the traditional ―golden triangle‖ approach (ACE inhibitors, beta-blockers, MRAs) in treating heart failure. For example, the 2021 American Diabetes Association guidelines recommended the use of SGLT2 inhibitors as primary therapy for type 2 diabetes who have Atherosclerosis-related cardiovascular disease, are deemed high risk, have LV failure, or have chronic kidney injury. Meanwhile, heart failure guidelines in the European

Society of Cardiology's 2021 introduced a ―quadruple therapy‖ strategy for HFpEF, combining SGLT2I with ACE inhibitors/ARNIs, beta-blockers, and mineralocorticoid receptor antagonists. This marks a significant departure from older protocols. **(Tomasoni et al., 2024)**

SGLT2-I in acute myocardial infarction

In one example study, researchers used both diabetic and non-diabetic rats whom were assigned randomly to a group of canagliflozin and a placebo group; over a four-week period, after inducing a myocardial infarction through coronary artery ligation. The results revealed that canagliflozin reduced the size of the infarcted area significantly compared to the placebo group. Interestingly, this benefit was not linked to changes in blood glucose levels but instead appeared to stem from the activation of specific cellular pathways, such as AMPK or JAK/STAT3. In a related study called Masashi Mizuno et al. which Explored the effect of empagliflozin on the Cardiomyocyte structure in the non-affected area of the heart post-myocardial infarction in rats with diabetes, They found that empagliflozin helped to restore the size and quantity of cardiac mitochondria and avoided an Too much decrease in mitochondrial volume following diabetic myocardial infarction through reestablishing autophagy and blocking reactive oxygen species clusters. **(Hua et al., 2023)**

According to Embody trial which investigated the Impact of the medication on the sympathetic nerve activity of the heart in patients with AMI and type II diabetes, there has been a marked improvement of both sympathetic and parasympathetic activities following use of empagliflozin. Additionally, SGLT2 were found to activate the AMP-activated protein kinase (AMPK) pathway, which helps reduce oxidative stress, promote autophagy, and stimulate mitochondrial biogenesis. These mechanisms collectively protect the heart from damage and may help mitigate the effects of myocardial infarction.

Given these findings, starting SGLT2I treatment early during hospitalization for AMI could become a critical therapeutic strategy. Studies like these highlight the protective role and potential mechanisms of SGLT2I in managing heart damage after a heart attack. **(Shimizu et al., 2020)**

SGLT2-I as a treatment of arrhythmia

In addition to the cardioprotective effects that has been discussed above, there might be a further explanation, diabetes mellitus is known to worsen the remodeling of atria, which can lead to atrial fibrillation (AF). Defects in the structure and function of mitochondrium further affects the atrial electrical and structural remodeling. In a 2019 Qingmiao Shao et al. study, the membrane potential and respiratory function of atrial mitochondria were improved by empagliflozin in rats with diabetes. It also

reduced atrial remodeling and fibrosis, which reduced the AF incidence. Moreover, Inflammatory responses are considered to be linked to the onset of AF, as a vicious cycle is created due AF increasing inflammatory markers. On the contrary, SGLT2I have been shown in many studies to decrease inflammation and oxidative stress, potentially breaking this cycle. **(Minciună et al., 2024)**

While SGLT2I show promise in treating AF, their effects on ventricular arrhythmias (VAs) and long-term arrhythmia outcomes remain unclear. More clinical research is needed to fully understand how SGLT2I causes AF.

Several studies have explored the link between SGLT2-I and cardiovascular Consequences, with most suggesting a lower risk compared to other diabetes medications. However, significant limitations impacted many of these studies, which led to complications in the interpretation of their findings. For instance, three studies were affected by immortal time bias, and people who had recently used the comparator medications were excluded from all of these studies due to the employment of new user designs. Such exclusions can limit how broadly the results apply to real-world populations and may introduce selection bias, especially considering the dynamic progression of type II diabetes treatment strategies, where patients often switch between other lines of treatments prior to the use of SGLT2 inhibitors. Furthermore, the lack of detailed data on how SGLT2-I specifically impact cardiovascular system constitutes yet another challenge. we compared the risks of MACE, its Elements, Overall mortality and heart failure associated with SGLT2-I versus dipeptidyl peptidase-4 (DPP-4) inhibitors among individuals with type II diabetes. The Canadian Network for Observational Drug Effect Studies (CNODES) conducted this investigation. **(Padda et al., 2023)**

Conclusion and Recommendations:

SGLT2 inhibitors are gaining significant attention due to their hypoglycemic, renal, and cardiovascular protective properties. However, more research is still needed to fully understand their safety and effectiveness. Despite this fact, SGLT2-I show great promise and should be considered as part of a comprehensive approach for the control of many risk factors and Ensuring the integrity of patients.

Studies have shown that SGLT2-I reduce cardiovascular death and Overall mortality (ACM) in heart failure patients and decreased ejection fraction (HFrEF). They also reduce the risk of hospital admissions due to heart failure in a wide scope of patients with type II diabetes (T2DM) and high risk of

cardiovascular disease, regardless of ejection fraction (EF). The benefits are most pronounced in patients at the greatest risk, where the absolute risk reduction is greatest.

Given these findings, we strongly recommend incorporating SGLT2-I into the standard treatment plan for eligible patients upon hospital discharge.

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