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SGLT2 INHIBITORS DECREASE CARDIOVASCULAR DEATH AND HEART FAILURE HOSPITALIZATIONS: A SYSTEMATIC REVIEW

Muhammad Iqbal Anand[1*], Chrisan Bimo Prayuda[2], Patrick Phillo[3], Daniel Setiawan Nathan[4], Tara Titian Maulidya[5], Endah Tri Widanarti[5], Vera Akmilia[5], Devita Nur Amelia[5], Alifa Puspita Pramasari[6], Agus Suprapto[6]

[1]Departement of Internal Medicine, Swadaya Gunung Jati University
[2]Departement of Internal Medicine, Bandung Islamic University
[3]Departement of Internal Medicine, Padjadjaran University
[4]Departement of Internal Medicine, Maranatha Christian University
[5]Departement of Internal Medicine, General Achmad Yani University
[6]Departement of Internal Medicine, Siti Aisyah Madiun General Hospital

Corresponding Author:-
m.iqbal.anand@gmail.com

Abstract

According to the World Health Organization (WHO), cardiovascular disease is the leading cause of death from noncommunicable diseases (NCDs). It is responsible for 17.5 million deaths, which accounts for 46% of all deaths caused by noncommunicable diseases. Additionally, 80% of these deaths occur in low-middle income countries, and it is anticipated that this number will rise to 23.6 million in 2030. SGLT2 inhibitors are currently indicated as first- or second-line therapies of type 2 diabetes mellitus (T2DM) in patients who have established cardiovascular disease, high or very high cardiovascular risk, renal illness, or heart failure. This is the case in both Europe and the United States of America. In individuals who already have heart failure, taking SGLT2 inhibitors lowers the overall mortality risk as well as the chance of death from cardiovascular causes. Patients who are at a higher risk of dying as a whole are the ones who have proved to benefit from this. It has been established that SGLT2 inhibitors reduce the risk of cardiovascular mortality as well as the rate of hospitalizations and urgent care visits that are associated with heart failure in a range of different populations.

Keyword: *Cardiovascular disease; Heart failure; Sodium-glucose cotransporter 2 (SGLT2) inhibitors.*

INTRODUCTION

T2DM patients have a two- to threefold increased risk of cardiovascular events in comparison to persons who do not have diabetes, and cardiovascular mortality is responsible for approximately 80 percent of all deaths. Patients with type 2 diabetes who have never had a MI have a mortality risk that is comparable to that of people who have never had diabetes but have had a MI. Even though hyperglycemia is the primary risk factor for microvascular complications, it is only a moderate risk factor for cardiovascular disease (CVD).[1,2]

Furthermore, interventional studies that focus on lowering plasma glucose in type 2 diabetes have only a minor effect on reducing the risk of CV disease. In addition, the improvement in CV risk reduction that is related with better glycemic control does not become apparent for several years.[2] The vast majority of people who have type 2 diabetes have moderate to severe insulin resistance. This condition is linked to various metabolic abnormalities, such as obesity, dyslipidemia, and hypertension, all of which are risk factors for cardiovascular disease.[3]

Coronary heart disease (CHD) has evolved as a useful operational term to refer to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction usually caused by a sudden reduction in coronary blood flow.[4,5] According to the World Health Organization (WHO), cardiovascular disease is the main cause of death from NCDs and causes 17.5 million deaths or 46% of all non-communicable disease deaths, 80% occurs in low-middle income countries, and this figure is expected to increase. to 23.6 million in 2030.[6]

The data estimates that 7.4 million deaths are heart attacks due to CHD and 6.7 million are strokes.[6] The costs associated with CHD are expected to rise from 47 million DALY in 1990 to 82 million DALY in 2020, with emerging nations accounting for 60 percent of this increase. Because of this, it is necessary for us to devise a strategy to enhance the patient's quality of life.[7,8]

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) are a new family of medications that have been shown to lower blood glucose levels by increasing the amount of glucose that is excreted in the urine. In addition to the glucose-lowering impact, they also provide benefits for the cardiovascular system and the kidneys. The mechanisms behind these benefits are presumably pleiotropic and include a reduction in blood pressure, volume depletion, weight loss, and many metabolic effects (such as lipolysis and synthesis of ketone bodies).[9,10]

SGLT2 inhibitors are currently indicated in both Europe and the United States of America as first- or second-line therapies of type 2 diabetes mellitus (T2DM) in patients who have established cardiovascular disease, high or very high cardiovascular risk, renal illness, or heart failure.[11] Recently, the usage of dapagliflozin has been expanded to include patients who have heart failure but do not have type 2 diabetes. This is due to new data showing advantages in this population.[12]

METHODS

The full-text publications published in English were utilised as the source material for the data that was acquired for the purpose of performing this systematic review. The review's objective was to determine whether or not a certain treatment is more effective than another. The aim of this paper is to assess the benefits of SGLT2 inhibitors in reducing cardiovascular death and heart failure hospitalization. The research involved is a five-year study from 2017 to 2022.

During the process of producing this article, the databases Pubmed and Google Schoolar were used in their respective capacities. Both controlled clinical trials and randomised clinical trials were included as part of the research project's component aspects as part of it. This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) paradigm, in which the researchers originally entered keywords into each database. Keyword for search the article : “SGLT2 inhibitors”; “cardiovascular death”; “heart failure” and “heart failure hospitalizations”.

The phrases ((“sodium glucose transporter 2 inhibitors”[Pharmacological Action] OR “sodium glucose transporter 2 inhibitors”[MeSH Terms] OR “sodium glucose transporter 2 inhibitors”[All Fields] OR (“sglt2”[All Fields] AND “inhibitors”[All Fields]) OR “sglt2 inhibitors”[All Fields]) AND (“decrease”[All Fields] OR “decreased”[All Fields] OR “decreases”[All Fields] OR “decreasing”[All Fields]) AND (“cardiovascular system”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “system”[All Fields]) OR “cardiovascular system”[All Fields] OR “cardiovascular”[All Fields] OR “cardiovasculars”[All Fields]) AND (“death”[MeSH Terms] OR “death”[All Fields] OR “deaths”[All Fields]) AND (“heart failure”[MeSH Terms] OR (“heart”[All Fields] AND “failure”[All Fields]) OR “heart failure”[All Fields]) AND (“hospital s”[All Fields] OR “hospitalisation”[All Fields] OR “hospitalization”[MeSH Terms] OR “hospitalization”[All Fields] OR “hospitalising”[All Fields] OR “hospitality”[All Fields] OR “hospitalisations”[All Fields] OR “hospitalised”[All Fields] OR “hospitalizations”[All Fields] OR “hospitalized”[All Fields] OR “hospitalize”[All Fields] OR “hospitalizing”[All Fields] OR “hospitals”[MeSH Terms] OR “hospitals”[All Fields] OR “hospital”[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) throughout the course of this research. The six articles that we received are going to be addressed during the conversation that will follow. **(Table 1)**.

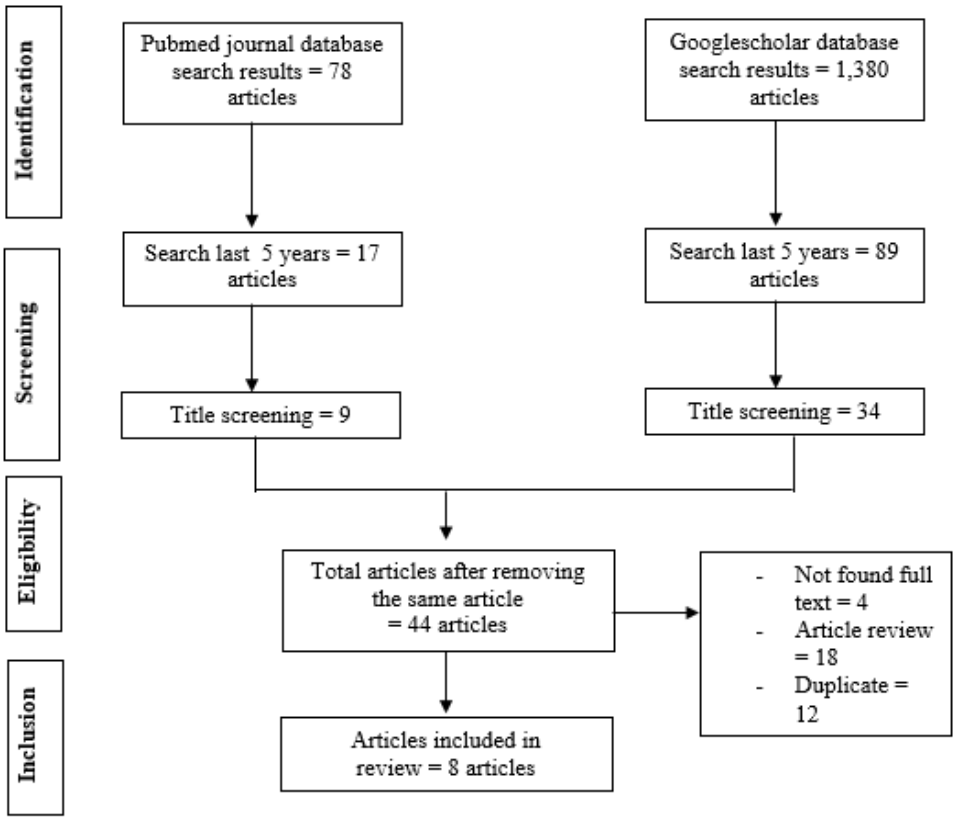

Figure 1. Article search flowchart

RESULT

A study conducted with licogliflozin 10 mg for 12 weeks decreased N-terminal pro–B-type natriuretic peptide (NT-proBNP) versus placebo (P =.033). They showed no difference was seen between licogliflozin and empagliflozin at 50 mg (P =.064), licogliflozin 50 mg (-0.58 ± 0.34%) and empagliflozin (-0.44 ± 1.18%) reduced glycated haemoglobin more than placebo (-0.04 ± 0.91%). Both licogliflozin 50 mg and empagliflozin reduced body weight by 2.15 ± 2.40 kg. licogliflozin 50 mg (-9.54 ± 16.88 mmHg) and empagliflozin (-6.98 ± 15.03 mmHg) reduced systolic blood pressure over placebo (-2.85 ± 11.97 mmHg). Hypotension (6.5%), hypoglycemia (8.1%), and poor diabetes management were minor AEs (1.6%). Diarrhea (4.9%) was lower than reported.[13]

Other study reported women, whites, hypertensives, and those with a history of cardiovascular disease were more likely to have HF at baseline (14.4%). At baseline, more of these individuals used RAAS blockers, diuretics, and -blockers (P0.001). Overall, cardiovascular mortality or hospitalised HF was decreased in those treated with canagliflozin compared with placebo (16.3 vs 20.8 per 1000 patient-years; HR, 0.78; 95% CI, 0.67-0.91), as did fatal or hospitalised HF (HR, 0.70; 95% CI, 0.55-0.89) and hospitalised HF alone (HR, 0.67; 95 percent CI, 0.52-0.87).[14]

The effect on cardiovascular mortality or hospitalised HF may be larger in individuals with a history of HF (HR, 0.61; 95% CI, 0.46-0.80) compared with those without HF at baseline (HR, 0.87; 95% CI, 0.72-1.06; P interaction =0.021). Other cardiovascular outcomes and important safety outcomes were comparable in persons with and without HF at baseline (all interaction P values >0.130), except for a possible lower absolute incidence of events attributed to osmotic diuresis in those with HF (P=0.03).[14]

Other project with partisipant average age was 63.3 ± 35.8% were female, the average duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. Canagliflozin significantly reduced the rate of the main outcome compared to placebo (hazard ratio [HR] = 0.86; 95% confidence interval [CI] = 0.75-0.97; P <0.001 for noninferiority; P = 0.02 for superiority; 26.9 vs. 31.5 participants per 1000 patient-years).[15]

Canagliflozin seems to slow the progression of albuminuria (HR = 0.73; 95% CI = 0.67 to 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 causes (HR = 0.60; 95% CI = 0.47-0.77). Except for an increased risk of amputation (6.3 vs. 3.4 per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75), all other adverse reactions were equivalent to canagliflozin.[15]

Packer, et al (2021) conducted a study for heart failure patient. They received an IV diuretic drug in an outpatient environment in the preceding 12 months, and to encounter a heart failure episode after randomization (all p <0.001). Empagliflozin reduced the risk of cardiovascular mortality or heart failure hospitalisation compared to placebo. It also improved health status and functional class. Despite recent volume overload patients' susceptibility to fluid retention, the extent of these advantages (even after 1 month of therapy) was not greater (interaction p >0.05).[16]

Wanner study with 2250 of 7020 patients treated had renal disease at baseline; 67% had type 2 diabetes for >10 years, 58% received insulin, and 84% used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In

patients with prevalent kidney disease at baseline, empagliflozin reduced cardiovascular death by 29% compared with placebo (HR = 0.71; 95% CI = 0.52-0.98, all-cause mortality by 24% (HR = 0.76; 95% CI = 0.59-0.99), HF hospitalisation by 39% (HR = 0.61; 95% CI = 0.42-0.87), and all-cause hospitalisation by 19% (HR = 0.81; 95% CI = 0.72-0.92).[17]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Agent Therapy	Result
Boer, 2020[13]	Spain	Prospective study; RCT	496 patients	Licogliflozin + empagliflozin 50 mg; licogliflozin 50 mg; and empagliflozin	Licoglifozin's ability to lower NT-proBNP levels hints to the possibility that individuals with type 2 diabetes and heart failure might benefit from SGLT1 and 2 inhibition.
Radholm, 2018[14]	Sweden	Prospective study; RCT	43,30 participants	Canagliflozin 100 mg	Canagliflozin lowered the risk of cardiovascular mortality or hospitalised HF across a wide range of patient subgroups. HF patients may benefit more.
Neal, 2017[15]	UK, USA, Canada, and other country	Prospective study; RCT	10,142 participants	Canagliflozin 100 mg	In two studies including individuals with type 2 diabetes and an elevated risk of cardiovascular disease, canagliflozin reduced the incidence of cardiovascular events but increased the chance of toe or metatarsal amputation.
Packer, 2021[16]	UK, USA, Canada, and other country	Prospective study; RCT	3,730 patients	Empagliflozin	Diuresis does not seem to have a dominating role in mediating the physiological changes or therapeutic effects of SGLT2 inhibitors on the progression of heart failure in patients who have a lower ejection fraction, according to the results of the studies taken as a whole.
Wanner, 2018[17]	UK, USA, Canada, and other country	Prospective study; RCT	7,020 patients	Empagliflozin	Patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic renal disease all benefited from treatment with empagliflozin, which led to better clinical outcomes and a reduction in mortality.
McMurray, 2019[18]	UK, Canada, and other country	Prospective study; RCT	2,373 patients	Dapagliflozin	Dapagliflozin reduces the risk of worsening heart failure or cardiovascular mortality in individuals with heart failure and a decreased ejection fraction, independent of diabetes.
Petrie, 2020[19]	UK, USA, Canada, and other country	Prospective study; RCT	4,744 patients	Dapagliflozin	In this exploratory analysis of a randomised trial of patients with HFrEF, dapagliflozin, in comparison with placebo, significantly reduced the risk of worsening heart failure or cardiovascular death when added to recommended therapy. This effect was seen regardless of whether or not the patients had diabetes.
Adamson, 2021[20]	UK, USA, Taiwan, and other country	Prospective study; RCT	4,744 patients	Dapagliflozin	In HFrEF, they found evidence of a phenomenon known as the "obesity survival paradox." They demonstrated that the benefits of dapagliflozin were seen throughout the whole spectrum of BMI that was investigated.

Another study used dapagliflozin in 2,373 heart failure patients. They showed 227 patients (9.6%) in the dapagliflozin group and 273 patients (11.5%) in the placebo group died from cardiovascular causes (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%) died from any cause (hazard ratio, 0.83; 95 percent CI, 0.71 to 0.97). Diabetes individuals had comparable findings as non-diabetic people. Volume depletion, renal failure, and hypoglycemia were equally common.[18]

Other study with 4,742 patients (mean age 66; 1109 [23%] women; 2605 [55%] without diabetes). The main outcome occurred in 171 of 1298 (13.2%) dapagliflozin-treated individuals and 231 of 1307 (17.7%) placebo-treated people without diabetes (HR = 0.73 [95% CI = 0.60-0.88]). In diabetic patients, the main outcome occurred in 215 of 1075 (20%) dapagliflozin patients and 271 of 1064 (25.5%) placebo patients (HR = 0.75 [95% CI, 0.63-0.90]; P =.80 for interaction). 53 of 438 patients (12.1%) in the dapagliflozin group and 71 of 419 (16.9%) in the placebo group had the main endpoint (HR = 0.67 [95% CI = 0.47-0.96]).[19]

In patients with a HbA1c of at least 5.7%, the main outcome occurred in 118 of 860 (13.7%) dapagliflozin patients and 160 of 888 (18%) placebo individuals (HR = 0.74 [95% CI = 0.59-0.94]; interaction P = 0.72). Volume depletion was recorded in 7.3% of dapagliflozin patients and 6.1% of placebo patients without diabetes, and 7.8% of dapagliflozin and 7.8% of placebo patients with diabetes. 4.8% of individuals in the dapagliflozin group and 6% in the placebo group without diabetes had a renal adverse event.[19]

Other study by Adamson, et al (2021) showed the unadjusted HR for the main outcome using obesity class 1, group with the lowest risk, as reference was as follows: under/normal-weight 1.41 (1.16-1.71), overweight 1.18 (0.97-1.42), and obesity class II/III 1.37. (1.10-1.72). Patients with obesity classified as class I had the lowest mortality risk overall. The

effect of dapagliflozin on the primary outcome and on other outcomes did not differ according to the participant's BMI at the beginning of study. For example, the HR for the primary outcome was as follows: under/normal-weight 0.74 (0.58-0.94), overweight 0.81 (0.65-1.02), obesity class I 0.68 (0.50-0.92), and obesity class II/III 0.71 (0.51-1.00) (p for interaction = 0.79). At the end of 8 months of treatment with dapagliflozin, patients saw a mean weight loss of 0.9 (0.7-1.1) kg (P <0.001).[20]

DISCUSSION

Antihyperglycemic medicines of the class known as sodium-glucose co-transporter-2 (SGLT-2) inhibitors operate on SGLT-2 proteins that are expressed in the renal proximal convoluted tubules. It does this by inhibiting the reabsorption of glucose that has been filtered into the tubular lumen, which is how it achieves its action. To this day, the Food and Drug Administration (FDA) has given its blessing to the use of canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, which are all SGLT-2 inhibitors, in the treatment of type 2 diabetes in adults. Although the guidelines for usage of each agent are different, all four agents have been given the green light for use in people who have been diagnosed with type 2 diabetes mellitus (DM) in order to enhance blood sugar management in addition to changes in diet and physical activity.[21]

Table 2. Hazard risk for readmission/hospitalization and death by agent

Study	Agent	Hospitalization	Mortality
Radholm, 2018	Canagliflozin 100 mg	0.67-0.70	0.78
Neal, 2017	Canagliflozin 100 mg		0.86
Packer, 2021	Empagliflozin	0.71	0.81
Wanner, 2018	Empagliflozin	0.61-0.80	0.71
McMurray, 2019	Dapagliflozin	0.70	0.82
Petrie, 2020	Dapagliflozin	0.75	0.73
Adamson, 2021	Dapagliflozin		0.74

On March 29, 2013, canagliflozin became the first SGLT-2 inhibitor to get approval from the Food and Drug Administration. In addition to changes in diet and activity levels, it is recommended for adult patients who have type 2 diabetes to take this medication in order to better regulate their blood glucose levels.[21] It is also indicated to reduce the risk of cardiovascular (CV) adverse events in type 2 DM subjects who already have an underlying CV illness, cardiovascular mortality, hospitalisation for heart failure, and increases in serum creatinine in type 2 DM patients who already have diabetic nephropathy and albuminuria.[14,15,22–24]

In January of 2014, the FDA gave their blessing to the use of dapagliflozin. In addition to changes in diet and activity levels, it is recommended for adult patients who have type 2 diabetes to take this medication in order to better regulate their blood glucose levels.[9,18,25] Other indications include reducing the risk of cardiovascular mortality and hospitalisation in adult subjects who already have heart failure, as well as having a decreased ejection fraction (EF) and being classified as having a New York Heart Association (NYHA) level of II-IV by the New York Heart Association.[26]

Patients with type 2 diabetes who have an underlying cardiovascular illness or several risk factors for cardiovascular disease are also candidates for this treatment. It is also recommended for patients with chronic kidney disease (CKD) who are at risk of progressive disease in order to reduce the risk of a continuing decline in their estimated glomerular filtration rate (eGFR), end-stage renal disease (ESRD), cardiovascular mortality, and hospitalisation for heart failure.[26]

Empagliflozin was the third SGLT inhibitor to acquire clearance from the FDA in August of 2014, following closely on the heels of dapagliflozin's success in gaining that approval. It is recommended for use in adult patients who have type 2 diabetes in order to improve blood glucose control in addition to diet and exercise, reduce the risk of cardiovascular adverse events in type 2 diabetes patients who have an underlying cardiovascular illness, and minimise the risk of cardiovascular mortality and heart failure hospitalisation in adult patients who have an underlying cardiovascular illness and decreased ejection fraction. Ertugliflozin is the most recent SGLT inhibitor to get clearance from the FDA. It was granted this approval in 2017, and it is suggested for use in adult subjects diagnosed with type 2 diabetes to enhance the management of blood glucose in addition to changes in diet and physical activity.[21]

In individuals who have heart failure, SGLT2 inhibitors lower the overall mortality rate, as well as the death rate from cardiovascular causes. SGLT2 inhibitors have been shown to lower the composite of cardiovascular mortality or HF hospitalizations/urgent visits across a number of different populations. These groupings include women, older patients, people of African American descent, and those who have poor renal function.[4,22,27]

Treatment with SGLT2 inhibitors seems to significantly reduce the risk of a composite outcome consisting of cardiovascular mortality or heart failure hospitalizations/urgent visits in patients who have heart failure with preserved ejection fraction (HFpEF). These findings provide support to the idea that SGLT2 inhibitors might become a new foundational component in the treatment of heart failure (HF).[10,17,28]

Multiple factors, such as ischemia brought on by epicardial coronary artery disease, microvascular dysfunction, myocyte hypertrophy, impaired mitochondrial function, dysautonomia, increased levels of proinflammatory cytokines, and sodium retention brought on by the up-regulation of sodium-glucose co-transporters, can all be attributed to the fact that diabetes can play a role in the onset or worsening of heart failure (HF).[29,30]

These effects, in conjunction with co-morbidities such as obesity, hypertension, and renal disease, may lead to subclinical myocardial dysfunction or heart failure with a decreased or retained ejection fraction. Before the discovery of SGLT2

inhibitors, glucose-controlling treatments for diabetes had either no impact on heart failure outcomes or a detrimental effect on patients.[29,30]

An improvement in oxygen supply, cardiac fuel energetics, and mitochondrial activity may occur as a result of SGLT2 inhibition, which works against some of the negative effects that diabetes and insulin resistance have on the metabolism and function of the cardiovascular system. Additionally, there are additional beneficial effects of SGLT2 inhibitors on the hemodynamics of HF that may be independent of DM. These include natriuresis and a reduction in preload, as well as beneficial effects on circulating provascular progenitor cells, a reduction in blood pressure and afterload, and regression of left ventricular hypertrophy. SGLT2 inhibitors may possibly contribute to better outcomes in heart failure by protecting the kidneys and causing weight reduction.[27,31]

CONCLUSION

SGLT2 inhibitors reduce the risk of death overall and from cardiovascular causes in patients who already have heart failure. This benefit is shown in patients who have a higher risk of dying overall. It has been demonstrated that SGLT2 inhibitors reduce the risk of cardiovascular mortality as well as the rate of heart failure hospitalizations and urgent care visits in a variety of diverse populations.

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