Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2021, 10(2):139-143
https://doi.org/10.51847/acxDC9hQpC

Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Cardiovascular Protection of Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) in Type 2 Diabetes Mellitus; Literature Review

Ziyad Ali Alsaedi[1]*, Khalid Mohammed Alahmadi[1], Abdulaziz Zakaria Khan[1], Ezzaddin Mugahed Alrait[1], Mohammed Khaled Al Ghamdi[1], Abdullah Mutrik Alqahtani[2], Hadil Ali Alkahmous[3], Rakan Saleh Alanazi[3], Anas Abdulrhman Aljohani[4], Wessam Ahmed Alsawyan[5], Faisal Ayed Almazariqi[6], Abdullah Oudah Saeed Al Jabal[7]

[1]Faculty of Medicine, Ibn Sina National College of Medicine, Jeddah, KSA.
[2]Faculty of Medicine, Prince Sattam bin Abdulaziz University, Riyadh, KSA.
[3]Faculty of Medicine, Imam Mohammed Bin Saud Islamic University, Riyadh, KSA.
[4]Department of Internal Medicine, King Fahad Hospital, AL Madinah, KSA.
[5]Faculty of Medicine, Qassim University, Qassim, KSA.
[6]Department of Family Medicine, Urwah Primary Health Care, Madinah, KSA.
[7]Department of Emergency, Al-namas Genral Hospital, Al-namas, KSA.

***Email:** dr.ziad00@gmail.com*

ABSTRACT

Diabetes mellitus is a significant risk factor for major adverse cardiovascular events and all-cause mortality. It is essential to control blood glucose levels, but a combination of controlled blood glucose and cardioprotective effect, mortality, and morbidity secondary to diabetes would be significantly reduced. Sodium-glucose co-Transporter 2 inhibitor provides great diabetic control in addition to protection against cardiovascular events, with or without increased cardiovascular risks. This narrative review aims to assess the efficacy and safety of SGLT2i in preventing cardiovascular consequences among patients with diabetes mellitus type-2. A search in the PubMed database was performed for relevant articles using the following Mesh words: Sodium-glucose co-transporter 2 inhibitor, an SGLT2 inhibitor, Cardiovascular protection, Cardiovascular events, myocardial infarction. SGLT-2 inhibitors were found to provide cardiovascular protection and decreased all-cause of death in addition to reasonable glycemic control compared to placebo. Several rare adverse effects were reported, but generally, all of them were affordable and well-tolerated. Further trials are recommended to establish SGLT-2 inhibitors concerning the risk of amputations.

Key words: *SGLT-2 inhibitor, Heart failure, Major adverse cardiovascular events, Cardiovascular risk*

INTRODUCTION

Diabetes mellitus carries a significant risk factor for morbidity and mortality worldwide with a burden contribution to healthcare cost [1-3]. Type-2 Diabetes mellitus (T2DM) is more common than other types and accounts for approximately 90-95% of all cases with ongoing rapid growth worldwide and in the USA [3, 4]. The increase in an unhealthy lifestyle, population aging, and obesity trends rate among adults and children may somewhat explain the diabetes increase in incidence and prevalence [3].

In 2017, it was estimated that the diabetes prevalence in the age group 20-79 years is 415 million, with 5 million deaths related to diabetes [5]. Further, the number of diabetes patients was expected to increase to 642 million by

© 2021 The International Journal of Pharmaceutical Research and Allied Sciences (IJPRAS). **Open Access** - This article is under the **CC BY NC SA** license (https://creativecommons.org/licenses/by-nc-sa/4.0).

2040 [5]. T2DM risk factors are a combination of both genetic and metabolic factors [4]. Of note, non-modifiable risk factors include family history, ethnicity, older age, and previous gestational diabetes [4]. On the other hand, modifiable risk factors include obesity, unhealthy food, sedentary lifestyle, and smoking [5].

T2DM is a chronic cardiometabolic disease associated with an increased risk of CVD, chronic kidney disease, and heart failure, all of which are linked to mortality, morbidity, reduced quality of life, and elevated healthcare cost [6]. CVD represents a great individual and societal burden in T2DM patients and is considered the primary cause of death in both type 1 and 2 diabetes mellitus [6, 7]. The life expectancy in T2DM is shorter than in non-diabetic patients, and still, with better modifiable risk factors control nowadays, a continuous decline in major cardiovascular events (MACE) has been recorded within the last two decades, in both the USA and Europe [6].

Nonetheless, CVD lethal outcomes are declined less among T2DM patients compared with non-diabetic patients [6]. Cardiovascular events were responsible for a higher death percentage in patients with T2DM than those with T1DM [7]. Moreover, diabetes represents a two-fold increase risk for major stroke subtypes, coronary heart disease, and deaths related to other vascular etiologies [8].

In a normal kidney function, the proximal tubules can transport around 500 g of glucose daily, leading to complete reabsorption of the filtered amount of glucose [9]. However, when the plasma glucose level exceeds 10 to 11.1 mmol/L, glucosuria is noticed [9]. Sodium-glucose cotransporter-2 is the major kidney transporter, accountable for approximately 97% of the transporting across the luminal membrane [9]. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are one of the antihyperglycemic agents used to control diabetes mellitus by effectively reducing renal glucose reabsorption and provoking glucosuria [10].

Several SGLT2i like ertugliflozin, dapagliflozin, sotagliflozin, canagliflozin, and empagliflozin are available in the market. Initial randomized clinical trials were performed to prove the cardiovascular safety of SGLT2i, and surprisingly found a profound cardiovascular events reduction, including hospitalization for heart failure in patients with diabetes mellitus and underlying atherosclerotic vascular disease and progression of chronic kidney disease in T2DM patients [6, 9]. Furthermore, dapagliflozin and empagliflozin are significantly beneficial in cardiovascular death in patients with New York Heart Association classes 2, 3, or 4 with or without T2DM or worsening heart failure [6].

MATERIALS AND METHODS

A search in the PubMed database was performed for relevant articles using the following Mesh words: Sodium-glucose co-transporter 2 inhibitor, SGLT2 inhibitor, Cardiovascular protection, Cardiovascular events, myocardial infarction.

In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics: Sodium-glucose co-transporter 2 inhibitor, SGLT2 inhibitor, Cardiovascular protection, Cardiovascular events, myocardial infarction. Exclusion criteria were all other articles, which did not have one of these topics as their primary endpoint.

Around 90 publications were chosen as the most clinically relevant out of 1,202 articles indexed in the previous two decades, and their full texts were evaluated. A total of 31 of the 90 were included after a thorough examination. Additional research and publications were found using reference lists from the recognized and linked studies. Expert consensus recommendations and commentary were added where relevant to help practicing physicians assess meningitis most simply and practically possible.

RESULTS AND DISCUSSION

SGLT2i effectively reduces postprandial and fasting glucose levels and lowers insulin demand without promoting hypoglycemia [11, 12]. Hence, lowering postprandial glucose and A1C leads to decrease cardiovascular events and all-cause mortality in patients with T2DM, according to a previous cohort study [13]. A recent large-scale randomized clinical trial has shown SGLT2i to reduce cardiovascular and renal fatal outcomes in T2DM patients and suggest that it might benefit those with T1DM as well [11]. In regards to the benefit of SGLT2i in T1DM, Yamada T. concluded that adding SGLT2i to insulin therapy in T1DM resulted in a significant reduction in HbA1C level and weight but increased the risk of diabetic ketoacidosis and genital infections [14]. Yet, the safety and adverse outcomes of SGLTi2 are discussed separately in this literature review.

Of note, SGLT2i confirmed cardiovascular and renal protection in T2DM patients with atherosclerotic cardiovascular risk in three large prospective placebo-controlled trials; CANVAS program with canagliflozin,

EMPAREG-OUTCOME with empagliflozin, and DECLARE-TIMI 58 with dapagliflozin [12]. Moreover, in a trial of T2DM patients with high cardiovascular risk who received empagliflozin, they had a lower rate of cardiovascular deaths, non-fatal stroke, and non-fatal myocardial infarction compared to the placebo group [15]. The findings mentioned was not associated with significant difference between two groups in the risk of myocardial infarction or stroke [15]. Additionally, the empagliflozin group had a lower risk of death from any cause and hospitalization for heart failure than the placebo group [15].

In the CANVAS program, two trials involving T2DM patients with high cardiovascular risks who received canagliflozin compared to a placebo effect [16]. The CANVAS program was concluded that canagliflozin reduced the risk of all three components of the primary outcome; non-fatal stroke, nonfatal myocardial infarction, and death related to cardiovascular events [16]. In addition, canagliflozin use was associated with a lower risk of hospitalization for heart failure, substantive loss of kidney function, and albuminuria development compared to those who received a placebo [16].

Contradictorily, dapagliflozin did not significantly lower MACE risk in T2DM patients, including cardiovascular death, myocardial infarction, and stroke [17]. Nevertheless, dapagliflozin was associated with preventing certain cardiovascular risks, especially hospitalization for heart failure, regardless of the atherosclerotic or heart failure history [17]. In addition to lowering hospitalization for heart failure, dapagliflozin was found to provide a lower rate of adverse renal outcomes, similarly to the other SGLT2i [17]. Accordingly, Zelniker. suggested that SGLT2i must be considered a first-line option in all T2DM patients, with or without cardiovascular disease, heart failure, or cardiovascular risk factors [18].

Cardioprotective mechanism of SGLT2i

The precise mechanism for which SGLT2i provide their protection against cardiovascular events is unknown [19]. Yet, several theses have been documented to explain the cardioprotective mechanism of SGLT2i; firstly, SGLT2i prevents the reabsorption of glucose and sodium in the proximal convoluted tubules, which resulted in diuresis outcome and increased urinary sodium excretion [19-21]. The diuresis outcome is the primary driver of heart failure and kidney benefits [19]. Secondly, by the inducing nutrient deprived state and glucose-lowering via SGLT2i, adipose tissue lipolysis consequently resulted in a generation of ketone bodies, for instance, β-hydroxybutyrate [19]. Subsequently, the result of decreased cellular stress and cellular sodium influx might provide some cardiovascular protection [19].

Furthermore, the SGLT2i effect is not limited to blood glucose improvement, but it also consistently lowers body weight (by improving caloric balance) and BP by influencing several vascular mediators of renal hemodynamics in both fasting and postprandial state [20, 21]. To illustrate, SGLT2i decreases atrial natriuretic peptide and insulin along with an increase in glucagon, renin-angiotensin-system components, and glucagon-like peptide 1 (GLP-1) [20].

Although the exact mechanism is still to be clarified, SGLT2i increases erythropoietin, hemoglobin, and hematocrit levels [19]. This can result in improving tissue oxygenation, including myocardium, leading to cardioprotection [19]. Finally, SGLT2i can indirectly demonstrate cardiovascular protection by improving the lipid profile and lowering uric acid levels, which subsequently reduces hypertension and CVD [21, 22].

Safety consideration

Regarding safety and adverse outcomes, SGLT2i was associated with a potential increase risk of amputation (particularly at the level of the toe or metatarsal), fractures, mycotic genital infections, and diabetic ketoacidosis, yet these adverse outcomes were infrequently reported [16, 23]. Further, in a correspondence study, SGLT2i was found shortly after initiation to be related to an increased risk of diabetic ketoacidosis; nevertheless, hospitalization secondary to diabetic ketoacidosis was infrequent [24].

Importantly, SGLT2i is considered a safe antidiabetic agent in regards to hypoglycemia, but increases the risk of genital infection, concluded by Secrest MH [21]. Eventually, oral administration of SGLT2i is considered a friendly and safe agent with good tolerability, and genital tolerability can be reduced by good hygiene and patient education [25].

CONCLUSION

Cardiovascular risk represents a significant impact on patients with type-2 diabetes mellitus. It can result in death from any cause, including chronic kidney disease, heart failure, myocardial infarction, and ischemic stroke.

Sodium-glucose co-transporter 2 inhibitor is a newly developed antidiabetic agent, demonstrating a significant cardioprotective effect in diabetic patients. However, the cardioprotective impact is limited to mainly three SGLT2i agents: empagliflozin, canagliflozin, and dapagliflozin. Further randomized trials on the other agents are recommended to establish their efficacy and safety profile. Generally, adverse outcome to SGLT2i is rare and affordable, and the benefit is considered to outweigh the risk overall.

ACKNOWLEDGMENTS : None

CONFLICT OF INTEREST : None

FINANCIAL SUPPORT : None

ETHICS STATEMENT : None

REFERENCES

1. Soep S, Agussalim A. The impact of health education about Diabetes mellitus on patient knowledge to control their Blood Sugar. J Adv Pharm Edu Res. 2020;10(3):141-5.
2. Alqahtiani NM, Alramadhan ZT, bin Obaid MR, Kurdi AN, Alhelal AA, Aljaafar FA, et al. Hypothyroidism in Saudi Arabia; Prevalence, risk factors, and its relation with Diabetes Mellitus. Arch Pharm Pract. 2020;11(3):56-63.
3. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and microvascular complications. Eur J Prev Cardiol. 2019;26(2_suppl):25-32.
4. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep. 2019;21(4):21. doi:10.1007/s11886-019-1107-y.
5. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50. doi:10.1016/j.diabres.2017.03.024.
6. Khunti K. SGLT2 inhibitors in people with and without T2DM. Nat Rev Endocrinol. 2021;17(2):75-6. doi:10.1038/s41574-020-00453-2.
7. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia. 2001;44(S2):S14-21.
8. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
9. Libianto R, Ekinci EI. New Agents for the Treatment of Type 2 Diabetes. Crit Care Clin. 2019;35(2):315-28. doi:10.1016/j.ccc.2018.11.007.
10. Kumar K, Kheiri B, Simpson TF, Osman M, Rahmouni H. Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Clinical Trials. Am J Med. 2020;133(11):e625-30. doi:10.1016/j.amjmed.2020.04.006.
11. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: Systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018;20(7):1755-61. doi:10.1111/dom.13260.
12. Scheen AJ. Cardiovascular and renal protection with sodium-glucose cotransporter type 2 inhibitors: new paradigm in type 2 diabetes management…and potentially beyond. Ann Transl Med. 2019;7(S3):S132.
13. Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, et al. Postprandial Blood Glucose Predicts Cardiovascular Events and All-Cause Mortality in Type 2 Diabetes in a 14-Year Follow-Up: Lessons from the San Luigi Gonzaga Diabetes Study. Diabetes Care. 2011;34(10):2237-43. doi:10.2337/dc10-2414
14. Egan AM, Montori VM. Review: In type 2 diabetes, SGLT-2 inhibitors or GLP-1 agonists reduce mortality vs control or DPP-4 inhibitors. Ann Intern Med. 2018;169(2) JC2. doi:10.7326/ACPJC-2018-169-2-002.
15. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. doi:10.1056/nejmoa1504720

16. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-57.
17. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.
18. Malaga G, Ruiz EF. SGLT-2 inhibitors for people with type 2 diabetes. Lancet. 2019;394(10198):559-60.
19. Salah HM, Al'Aref SJ, Khan MS, Al-Hawwas M, Vallurupalli S, Mehta JL, et al. Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomes-Systematic review and meta-analysis of randomized placebo-controlled trials. Am Heart J. 2021;232:10-22. doi:10.1016/j.ahj.2020.10.064.
20. Tonneijck L, Muskiet MH, Smits MM, Van Bommel EJ, Heerspink HJ, Van Raalte DH, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017;28(4):1023-39.
21. Secrest MH, Udell JA, Filion KB. The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. Trends Cardiovasc Med. 2017;27(3):194-202.
22. Custodio JS Jr, Duraes AR, Abreu M, Albuquerque Rocha N, Roever L. SGLT2 inhibition and heart failure-current concepts. Heart Fail Rev. 2018;23(3):409-18. doi:10.1007/s10741-018-9703-2.
23. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-9. doi:10.1016/S0140-6736(18)32590-X.
24. Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. N Engl J Med. 2017;376(23):2300-2. doi:10.1056/NEJMc1701990.
25. Zelniker TA, Wiviott SD, Raz I, Sabatine MS. SGLT-2 inhibitors for people with type 2 diabetes – Authors' reply. Lancet. 2019;394(10198):560-1.