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AN OVERVIEW OF ERTUGLIFLOZIN IN TREATMENT OF DIABETES MELLITUS

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ABSTRACT

A family of oral medications known as SGLT2 inhibitors has shown little success in treating type 2 diabetes. Enthusiastically belonging to the sodium-glucose cotransporter-2 (SGLT2) family, ertugliflozin is a new pharmacological approach to the management of type 2 diabetes patients. Lowering the risk of cardiovascular complications associated with diabetic mellitus (DM), kidneys, microvascular system, and macrovascular system is its main goal. It does not require insulin to function; instead, it raises glucose excretion in urine. The direct action on the kidneys by these medications constitutes a new paradigm in treatment. Hypoglycemia is a small concern, but pancreatic beta cell overstimulation is not scientific studies have shownthe use of SGLT-2 inhibitors can reduce the risk of Cardio vascular disease (CVD) in diabetics. Knowing how ertugliflozin affects the kidneys is crucial. It is recommended by the FDA to increase the starting dose from 5 mg oncea day up to 15 mg once a day in cases when tighter management of blood sugar is necessary, provided that the medication is well-tolerated. Among ertugflozin's most common adverse effects include hypovolemia and UTIs. Ertugliflozin can help type 2 diabetes patients when used with other drugs since it has a synergistic effect.

KEYWORDS: SGLT-2 inhibitor, Ertugliflozin, type 2 diabetes, CVD.

INTRODUCTION

Globally, diabetes is the most serious health issue. This disorder arises from persistently high blood glucose levels. Because they prevent the pancreas' beta cells from producing enough

insulin or from producing insulin that is either inefficient or fails to work properly. Now, of the several forms of diabetes, A family of oral medications known as SGLT2 inhibitors has had limited success in its usage to treat type 2 diabetes. Enthusiastically belonging to the sodium-glucose cotransporter-2 (SGLT2) family, ertugliflozin is a new pharmacological approach to the management of type 2 diabetes patients. Its primary objective is to mitigate the negative effects of diabetic mellitus (DM). on the cardiovascular system. Which is a rise in blood glucose concentration and a common complication of uncontrolled diabetes. Multiple studies have shown that diabetics are more likely to get infections of the lower respiratory tract, pneumonia, urinary tract, and soft skin. Infection treatment results in diabetic individuals are likely to be subpar, and the patient has an elevated chance of financial hardship.

ERTUGLIFLOZIN

The sodium-glucose cotransporter-2 (SGLT2) family includes the innovative medicine ertugliflozin, which is used to treat type 2 diabetes mellitus (T2DM). Reducing diabetic complications affecting the cardiovascular, renal, microvascular, and macrovascular systems is the main objective. On January 25, 2018, ertugliflozin, a medicine used orally to aid in the management of blood glucose levels in patients with type 2 diabetes mellitus (T2DM), was authorized or licensed by various regulatory agencies in Europe and Asia, including the National Medical Product Administration and the European Medicines Agency.[1-2]

Diabetic complications, including coronary arteriosclerosis, diabetes acidosis, and hypoglycemia, pose serious worldwide health risks; inhibiting SGLT2 can enhance glucose excretion in the urine, and insulin independentlylowers or blocks plasma glucose levels. Worldwide, type 2 diabetes is becoming an increasingly pressing health concern. One very specific inhibitor of class SGLT2 is ertugliflozin, a medication for the treatment of type 2 diabetes that has been approved by the US Food and Drug Administration.[3]

To manage type 2 diabetes, a new class of oral drugs called SGLT2 inhibitors has emerged. The canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin classes of drugs are as follows. Ertugliflozin is the most modern and widely used (SGLT2) inhibitor. The agencies have also given their stamp of approval to the fixed dose of the medication ertugliflozin.[4-5]

When taken orally, ertugliflozin has a bioavailability of about 100% and gets its maximum concentration when the patient is fasting for at least two hours after taking it. The medicine

reaches steady-state concentration in the body after an overdose during therapy, Additionally, those who suffer from type 2 diabetes experience a half-life of 16.6 hours.[6]

There is known to be little cytochrome P450-mediated metabolism of ertugliflozin since it is converted into two inert glucuronides by O-glucuronidation mediated by uridine diphosphate glucuronosyltransferase (UGT)1A9 and UGT 2B7.[7]

MECHANISM OF ACTION OF ERTUGLIFLOZIN A DRUG OF CLASS SGLT2 INHIBITORS

Selectively and effectively, SGLT2 inhibitors block SGLT2.[8]

Housed in the proximal convoluted renal tubule, the SGLT2 transporters possess a high capacity but a low affinity. They are in charge of reabsorbing 90% of the glucose from filtered plasma. Reducing hyperglycemia and promoting glucose excretion in urine, By obstructing SGLT2, The kidneys' ability to reabsorb glucose and salt that has been filtered is simply limited.[9]

One drug, canagliflozin, has shown substantial cross-reactivity with SGLT1 in clinical trials; the other drugs had IC50 values of 4.4 nM for SGLT2 and 684 nM for SGLT1. Compared to other SGLT2 inhibitors, empagliflozin (1.6 mg), ertugliflozin (1,960 mg), and dapagliflozin (803 mg) had lower SGLT1 half-maximal inhibitory concentrations. However, Sotagliflozin inhibits not one but two SGLT enzymes, making it a dual SGLT inhibitor.[10]

TThe SGLT2 inhibitors are a novel kind of medication that targets the kidneys directly. and do not rely on insulin sensitivity for their activity. Pancreatic beta cell overstimulation is not a concern, and hypoglycemia is just a small possibility.[11]

Inhibiting SGLT2 may have additional effects such as reduced albuminuria, reduced weight, altered lipid metabolism, elevated hemoglobin levels, reduced oxygen consumption, and reduced cellular glucotoxicity. Aside from enhancing mitochondrial activities. Pro-inflammatory cytokines such as IL-6, TNF, IFN, NF-, TLR-4, and TGF- seem to have their levels reduced by SGLT2 inhibitors.[12]

THE EFFECT AND SOME OUTCOMES OFTHE DRUG ERTUGLIFLOZIN ON:-

CARDIOVASCULAR

TThe management of diabetic consequences, including cardiovascular disease (CVD), remains a major obstacle. Diabetes patients on SGLT-2 inhibitors have a reduced risk of cardiovascular disease (CVD), according to scientific research. So, it's clear that drugs that lower blood sugar levels represent a huge improvement.[9]

Glucosuria is an independent renal activity of SGLT-2 inhibitors that lower glucose levels; this effect is independent of insulin. Therefore, they promote weight loss rather than hypoglycemia. Glucotoxicity is reduced, which in turn improves insulin sensitivity and β-cell activity.[10]

Patients on SGLT2 inhibitors were far less likely to experience atrial arrhythmias and end-cardiac events than those in the control group. Neither group had a substantially different rate of ventricular arrhythmias, sometimes known as the "cardiac arrest" component of SCD.[11]

Cardiac arrhythmias and failure were less common in patients on SGLT2 inhibitors for type 2 diabetes. If the antiarrhythmic effect of SGLT2 is medication- or class-specific, then more research is required to establish it.[12]

Regardless, type 2 diabetics had a decreased rate of fatal cardiovascular (CV) events compared to controls, while still being at a much higher risk than non-diabetics.[12-13]

Clinical research comparing the efficacy of ertugliflozin and empagliflozin to that of newer kinds of SGLT-2 inhibitors has been shown to lower the risk of cardiovascular complications in individuals with diabetes. Compared to linagliptin and saxagliptin. There has to be more research into what causes heart failure and non-diabetic cardiac issues.[14]

Using type 2 diabetics as a population, four large-scale studies examined the cardiovascular effects of ertugliflozin, dapagliflozin, empagliflozin, and canagliflozin. The examinations Two studies looked into the effects of canagliflozin and empagliflozin on diabetes mellitus type 2 (T2DM): the EMPA-REG OUTCOME study and the CANVAS PROGRAMME (Canagliflozin Cardiovascular Assessment Study).[12-13-7] Three major adverse cardiac events (MACEs)—nonfatal myocardial infarction, cardiovascular mortality, and nonfatal stroke—did not alter when ertugliflozin was statistically examined. A 30% reduction in HF-related hospitalizations, however, was linked to it.[7-14]

Ertugliflozin protects the heart using osmotic diuresis. Patients with heart failure may also benefit from reduced oxygen consumption and an increase in cardiac preload and afterload brought about by decreased plasma volume. The heart muscle receives more oxygen as the hematocrit level rises. An increase in erythropoietin production or a reduction in plasma volume could be responsible for this increase. SGLT2 inhibitors have several positive effects on the metabolism and heart, but they also lower weight and blood pressure.[15-16]

RENAL

Knowing how ertugliflozin affects the kidneys is crucial. The calorie deficit caused by less glucotoxicity and more glucosuria appears to have initiated a cascade of metabolic changes. The kidneys, arteries, retina, heart, and fat might all be protected from oxidative stress, endothelial dysfunction, swelling, and fibrosis if this works. The reno-protective effects of ertugliflozin are due to its ability torevive glomerular feedback in tubules. This, in turn, hyperfiltration, albuminuria, shear force, intra-glomerular pressure, and glucose and salt reabsorption from the proximal convoluted tubule are all decreased.[17-18]

Additional physiological effects, such as natriuresis, are observed with SGLT2 inhibitors outside of the effects on BP and kidney function. For people who have type 2 diabetes and developed diabetic nephropathy, ertugliflozin lowers the albumin/creatinine ratio and decreases the risk of renal failure. The kidneys fail, the patient undergoes renal replacement treatment, and the patient's renal filtering ability significantly decreases (e.g., their blood creatinine levels double or As time goes on, their eGFR (estimated glomerular filtration rate) decreases by 40%.).[19-20]

Using 5 mg and 15 mg of ertugliflozin a cohort trial with a mixed-status ertugliflozin population and a pre-determined exploratory composite renal endpoint analysis, David Z. I. Cherney et al. Changes in the treatment group's eGFR with time, as well as changes in albuminuria and albuminuria status, are also documented. Both the whole population and subgroups separated by renal function at baseline were analyzed in every way. Using two subgroups of baseline eGFR and Using the Acute Renal Failure Standard Medical Dictionary for Regulatory Activities Query (SMQ), researchers examined the prevalence of adverse events associated with acute renal failure.The renoprotective effects of ertugliflozin have also been discovered.[20]

A lower glomerular filtration rate (GFR), Chronic kidney disease (CKD), high blood pressure, heart disease, persistent albuminuria, and hypertension are all outcomes of type 2 diabetes mellitus. When SGLT2 inhibitors are used alongside anti-hypertensive medicines, blood pressure is successfully lowered. There is an increasing amount of research that shows that renal endpoints have been incorporated in several cardiovascular outcomes trials (CVOTs). and that these drugs may have reno-protective benefits in type 2 diabetes patients. Many ongoing studies examining renal outcomes will provide light on whether or not SGLT2 inhibitors have a therapeutic impact in slowingkidney disease progression in individuals with type 2 diabetes.[22-23]

APPROVALS AND RECOMMENDATIONS

When used with other lifestyle changes, such as a balanced diet and frequent exercise, ertugliflozin canhelp persons whose blood sugar levels are controlled by type 2 diabetes. Both the FDA and the EMA gave their stamp of approval to the drug in 2017 and early 2018, respectively. It is advised by the FDA to start with a higher dose than 5 mg once a day. to 15 mg once daily if more glycemic control is required, provided that the medication is well-tolerated. Never start ertugliflozin medication if your eGFR falls between the range of 30–60 mL/min/1.73 m2 or is lower than 30 mL/min/1.73 m2, as mentioned in.[24]

For people who have ASCVD, HF, and CKD simultaneously, SGLT2 inhibitors are offered as a recommendation by the American Diabetes Association (ADA). A drug that blocks SGLT2, such as empagliflozin or canagliflozin, with favorable CV outcome data, is recommended by the ADA in cases where ASCVD is common.[25] The American Diabetes Association suggests canagliflozin, dapagliflozin, or empagliflozin, three SGLT2 inhibitors with good HF outcome evidence if HF is present.[25] If chronic kidney disease is a big issue, Experts recommend SGLT2 inhibitors like canagliflozin, dapagliflozin, or empagliflozin because of their positive effects on the kidneys. as they all help postpone the course of CKD.[25] The most recent treatment guidelines for type 2 diabetes, published in 2020 by the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE), strongly suggest the use of drugs that inhibit SGLT2.

People with certain health issues are more likely to suffer from heart failure (characterized by a reduced ejection fraction) and cardiovascular disease (CVD): Advanced ischemic heart disease (ASCVD), or stage 3 chronic kidney disease (CKD): (CKD) use SGLT2 inhibitors because of their proven ability to prevent CV events.[26] Canagliflozin, dapagliflozin, and

empagliflozin are the SGLT2 inhibitors that have been recommended here due to their effectiveness in reducing the risk of renal and cardiovascular events. Their policy is not to recommend a particular SGLT2 inhibitor in situations where neither cardiovascular disease nor these recognized co-morbidities provide an increased risk. When alternative SGLT2 inhibitors (such as ertugliflozin) have neutral results, it is recommended to utilize SGLT2 drugs with positive CV and renal outcomes instead. This recommendation is made in both recommendations.

ADVERSE EFFECTS

Recently, phase III trials assessing ertugliflozin's safety have been conducted for type 2 diabetes as either a monotherapy or combo treatment. The maximum number of cases of symptomatic hypoglycemia reported in a single ertugliflozin study was 19.2% with glimepiride starting dosage 1 mg, 7–10% with 5 mg of ertugliflozin and 15 mg of ertugliflozin, respectively. Symptomatic hypoglycemia and GMIs in women (1.4 percent at 1 mg glimepiride, 7.7 percent at 5 mg ertugliflozin, and 10% at 15 mg ertugliflozin) and men (zero percent at 1 mg glimepiride, 2.1 percent at 5 mg ertugliflozin, and 4.4 percent at 15 mg ertugliflozin) were among the other adverse events.[27] Clinical investigations have shown that GMIs are the most prevalent side effect in both sexes. Patients using ertugliflozin should be informed about this adverse effect and kept under close observation during therapy. In most clinical trials, In contrast to the placebo group, the active treatment group saw a reduced occurrence of symptomatic hypoglycemia, UTIs, and hypovolemia. Taking insulin or sulfonylurea with an SGLT2 inhibitor can lower your risk of symptomatic hypoglycemia. Inhibitors of SGLT2 do not raise the danger of symptomatic hypoglycemia when used with other medications that reduce blood sugar. According to the available data. Rare cases of hypovolemia can be treated by modifying the dosing of diuretics and antihypertensive medications in high-risk individuals. Amputation was found in one canagliflozin study, but no other SGLT2 inhibitor has demonstrated this risk beyond observational data. Acute kidney damage was documented in several early observational studies; nevertheless, the Latest research lends credence to the notion that SGLT2 inhibitors may save the kidneys from harm. In rare cases, SGLT2 inhibitors may cause type 2 diabetics to have euglycemic diabetic ketoacidosis (DKA). One study found a frequency of 0.16 to 0.76 cases of DKA per 1000 patient years.[28] This is at odds with the results of a canagliflozin trial, which indicated that DKA occurred in 10% of type 1 diabetic individuals exposed to SGLT2 inhibitors.[29] Clinical studies have demonstrated that ertugliflozin and other Reduced blood pressure and weight

reduction are side effects of SGLT2 inhibitors. It is important to thoroughly monitor patients who have normal weight or blood pressure before beginning medication, as these additional advantages may vary from patient to patient.

ERTUGLIFLOZIN IN CONJUNCTION WITH OTHER MEDICATIONS

Ertugliflozin can help type 2 diabetes patients when used with other drugs since it has a synergistic effect. An example of such a drug is sitagliptin, which is sold under the brand name STEGLUJAN together with ertugliflozin.

Both ertugliflozin and sitagliptin are considered to be class 1 medications by the Biopharmaceutical Classification System. These two antihyperglycemic drugs are a formidable combination due to their unique but complimentary modes of action and exceptional safety profiles., which, when used together, reduce blood sugar levels more effectively than either drug alone. This approach is anticipated to have positive clinical effects for type 2 diabetics whose condition cannot be managed with metformin alone. People with poorly controlled type 2 diabetes who used metformin with ertugliflozin saw improvements in their glycemic control, hypertension, and weight loss.[30]

Table 1: Advantages and disadvantages of ertugliflozin.

Advantages of ertugliflozin	Disadvantages of ertugliflozin
Reduced blood pressure	Blood sugar in urine
No risk of hypoglycemia	Enhanced low-density lipoprotein
Cardiac and renal protective	Increased risk of diabetic ketoacidosis

CONCLUSION

The FDA approved the new SGLT-2 inhibitor ertugliflozin in December 2017 for the treatment of type 2 diabetes mellitus in adults. Glucose excretion in urine is enhanced by this insulin-dependent process. Clinical research has shown that it is safe, and improves both A1C and weight reduction. Reducing the risk of diabetes mellitus complications primarily protects the heart and kidneys. Patients with cardiovascular disease and chronic renal illness have a decreased risk of adverse events when they use ertugliflozin. You can use ertugliflozin without worrying on top of existing health issues if you suffer from type 2 diabetic mellitus like heart disease or kidney illness.

REFERENCES

1. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med [Internet], 2020; 383(15): 1425–35. Available from: http://dx.doi.org/10.1056/nejmoa2004967
2. Marrs JC, Anderson SL. Ertugliflozin in the treatment of type 2 diabetes mellitus. Drugs Context [Internet], 2020; 9: 1–10. Available from: http://dx.doi.org/10.7573/dic.2020-7-4
3. Yang J. Ertugliflozin for treatment of patients with Type 2 diabetes mellitus. Expert Rev Clin Pharmacol [Internet], 2018; 11(8): 747–53. Available from: http://dx.doi.org/10.1080/17512433.2018.1503051
4. Pfizer.com. [cited 2024 Jan 24]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/fda_approves_sglt2_inhibitor_
5. Medscape.com. [cited 2024 Jan 24]. Available from: https://www.medscape.com/viewarticle/891860.
6. Birkeland KI, Bodegard J, Eriksson JW, Norhammar A, Haller H, Linssen GCM, et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: A large multinational cohort study. Diabetes Obes Metab [Internet], 2020; 22(9): 1607–18. Available from: http://dx.doi.org/10.1111/dom.14074
7. MMontana M, Escalada J, Merchant Á, Reyes R, Rozas P. Prevention of cardiorenal complications with sodium–glucose cotransporter type 2 inhibitors: A narrative review. Diabetes Ther [Internet], 2022; 13(S1): 5–17. Available from: http://dx.doi.org/10.1007/s13300-022-01277-1
8. Van Bommel EJM, Muskiet MHA, Tonneijck L, Kramer MHH, Nieuwdorp M, van Raalte DH. SGLT2 inhibition in the diabetic kidney—from mechanisms to clinical outcome. Clin J Am Soc Nephrol [Internet], 2017; 12(4): 700–10. Available from: http://dx.doi.org/10.2215/cjn.06080616
9. Hummel CS, Lu C, Loo D, Hirayama BA, Voss AA, Wright EM. Glucose transport by human renal Na+/D-glucose cotransporters SGLT1 and SGLT2. Am J Physiol - Cell Physiol [Internet], 2011; 300: 14–21. Available from: http://dx.doi.org/10.1152/AJPCELL.00388.2010/ASSET/IMAGES/LARGE/ZH00011164920007.JPEG
10. Evenepoel P, Meijers B, Masereeuw R, Lowenstein J. Effects of an SGLT inhibitor on the production, toxicity, and elimination of gut-derived uremic toxins: A call for additional evidence. Toxins (Basel) [Internet], 2022; 14(3): 210. Available from: http://dx.doi.org/10.3390/toxins14030210

11. Nauck M. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther [Internet], 2014; 1335. Available from: http://dx.doi.org/10.2147/dddt.s50773
12. Fonseca-Correa JI, Correa-Rotter R. Sodium-glucose cotransporter 2 inhibitors mechanisms of action: a review. Front Med [Internet], 2021; 8. Available from: http://dx.doi.org/10.3389/FMED.2021.777861/BIBTEX
13. Abdul-Ghani MA, Norton L, DeFronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev [Internet], 2011; 32(4): 515–31. Available from: http://dx.doi.org/10.1210/er.2010-0029
14. Scheen AJ, Paquot N. Metabolic effects of SGLT-2 inhibitors beyond increased glucosuria: A review of the clinical evidence. Diabetes Metab [Internet], 2014; 40(6): S4–11. Available from: http://dx.doi.org/10.1016/s1262-3636(14)72689-8
15. Markwerth P, Bajanowski T, Tzimas I, Dettmeyer R. Sudden cardiac death—update. Int J Legal Med [Internet], 2021; 135(2): 483–95. Available from: http://dx.doi.org/10.1007/s00414-020-02481-z
16. Fernandes GC, Fernandes A, Cardoso R, Penalver J, Knijnik L, Mitrani RD, et al. Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: A meta-analysis of 34 randomized controlled trials. Heart Rhythm [Internet], 2021; 18(7): 1098–105. Available from: http://dx.doi.org/10.1016/j.hrthm.2021.03.028
17. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med [Internet], 2017; 376(15): 1407–18. Available from: http://dx.doi.org/10.1056/nejmoa1608664
18. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. Circ Res [Internet], 2018; 122(10): 1439–59. Available from: http://dx.doi.org/10.1161/circresaha.117.311588
19. 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 [Internet], 2017; 377(7): 644–57. Available from: http://dx.doi.org/10.1056/nejmoa1611925
20. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart [Internet], 2021; 107(13): 1032–8. Available from: http://dx.doi.org/10.1136/heartjnl-2020-318060

21. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors. J Am Coll Cardiol [Internet], 2020; 75(4): 422–34. Available from: http://dx.doi.org/10.1016/j.jacc.2019.11.031
22. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney Int [Internet], 2018; 94(1): 26–39. Available from: http://dx.doi.org/10.1016/j.kint.2017.12.027
23. Heerspink HJL, Karasik A, Thuresson M, Melzer-Cohen C, Chodick G, Khunti K, et al. Kidney outcomes associated with the use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol [Internet], 2020; 8(1): 27–35. Available from: http://dx.doi.org/10.1016/s2213-8587(19)30384-5
24. Cherney DZI, on behalf of the VERTIS CV Investigators, Charbonnel B, Cosentino F, Dagogo-Jack S, McGuire DK, et al. Effects of ertugliflozin on kidney composite outcomes, renal function, and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomized VERTIS CV trial. Diabetologia [Internet], 2021; 64(6): 1256–67. Available from: http://dx.doi.org/10.1007/s00125-021-05407-
25. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium-glucose cotransporter-2 inhibition in heart failure: Potential mechanisms, clinical applications, and summary of clinical trials. Circulation [Internet], 2017; 136(17): 1643–58. Available from: http://dx.doi.org/10.1161/circulationaha.117.030012
26. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomized, placebo-controlled trial. Lancet Diabetes Endocrinol [Internet], 2017; 5(8): 610–21. Available from: http://dx.doi.org/10.1016/s2213-8587(17)30182-1
27. Koro CE, Lee BH, Bowlin SJ. Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. Clin Ther [Internet], 2009; 31(11): 2608–17. Available from: http://dx.doi.org/10.1016/j.clinthera.2009.10.020
28. Giugliano D, Longo M, Scappaticcio L, Bellastella G, Maiorino MI, Esposito K. SGLT-2 inhibitors and cardiorenal outcomes in patients with or without type 2 diabetes: a meta-analysis of 11 CVOTs. Cardiovasc Diabetol [Internet], 2021; 20(1). Available from: http://dx.doi.org/10.1186/s12933-021-01430-3

29. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *standards of Medical Care in diabetes—2020*. Diabetes Care [Internet], 2020; 43(Supplement_1): S98–110. Available from: http://dx.doi.org/10.2337/dc20-s009
30. Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive Type 2 diabetes management algorithm – 2020 executive summary. Endocr Pract [Internet], 2020; 26(1): 107–39. Available from: http://dx.doi.org/10.4158/cs-2019-0472.