6-1-2021

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Introduction

Sodium Glucose Co-Transporter 2 inhibitors (SGLT2i), which include canagliflozin, dapagliflozin, empagliflozin and ertugliflozin, are insulin-independent oral antihyperglycaemic medications that uniquely reduce glucose reabsorption in the proximal convoluted tubules of the kidney resulting in glycosuria and natriuresis. These drugs are effective in the treatment of any stage of type 2 diabetes, as they can be used in states of insulin resistance and beta-cell dysfunction. There are a number of different SGLTi available worldwide (see Table 1). In Pakistan, we currently have dapagliflozin and empagliflozin licensed by the Drug Regulation Authority of Pakistan for use in diabetes. This paper aims to summarize unconventional non diabetic uses of SGLT2i that shown promising results.[1]

Table-1: List of available SGLT2i worldwide and their respective year of approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)[2,3]

SGLT2i	Body of Approval for Diabetics	Year of Approval
Dapagliflozin	FDA	2014
	EMA	2012
Canagliflozin	FDA	2013
	EMA	Pending
Empagliflozin	FDA	2014
	EMA	2014
Ertugliflozin	FDA	2017
	EMA	2017

Use of SGLT2 inhibitors in Diabetes

The 2019 guidelines from the American Diabetes Association recommend lifestyle modifications and metformin as first line treatment to reach target HbA1c in patients with type 2 DM; if these therapies fail to achieve goal then existing comorbidities should be considered including cardiovascular disease, congestive heart failure, chronic kidney disease and obesity to guide the decision for treatment. SGLT2i are recommended as preferred adjunct therapy in these four conditions, if the patient has an adequate estimated glomerular filtration rate (eGFR)[4-7] as SGLT2i have demonstrated multiple beneficial effects along with glucose lowering in a number of clinical trials.[5-7]

Sodium Glucose Co-Transporter 2 (SGLT2) is an essential protein primarily responsible for physiological glucose reabsorption. It is responsible for 90 percent of glucose uptake from proximal renal tubules, with SGLT1 reabsorbing the remaining 10%. Inhibition of SGLT2 results in blockage of this glucose reabsorption mechanism, causing glycosuria and resulting lowered blood glucose levels.[8] A distinct benefit with their use is that their glucose lowering effect is independent of beta cell function or insulin sensitivity thus carrying low risk for hypoglycaemia as well as potential for use in Type 1 Diabetics (approved in Europe, rejected in the US by FDA).[9] Since their introduction into clinical practice in 2013, SGLT2i drugs have demonstrated improved glucose control, reduced blood pressure, significant reductions in HbA1c, and weight loss in persons with type 2 diabetes.

Recent studies assessing the effects of SGLT2i on associated cardiac and renal disease in diabetic patients have shown cardiovascular risk reduction, decreased heart failure mortality and renal protective effects.[10-12] EMPA-REG OUTCOME was the first trial on the renal benefits in these drugs—published in 2016—showing that empagliflozin was associated with a slower progression of chronic kidney disease and fewer renal complications in type 2 DM patients with high cardiovascular risk.[10] EMPA-REG also demonstrated reduced cardiovascular complications with empagliflozin, with a 38 percent risk reduction from cardiovascular-related deaths in type 2 diabetics.[11] Dapagliflozin demonstrated reductions in cardiovascular hospitalizations and deaths in the DECLARE-TIMI trials.[12] Due to the success of SGLT2i in these settings, they are being considered for their potential cardiovascular benefits in nondiabetics as well.

SGLT2i and Cardiovascular Outcomes

All SGLT2i have demonstrated significant risk reduction in hospitalization for heart failure[13] yet a class effect on major cardiovascular events (in studies so far) has not been seen. According to the DAPA-HF trial, dapagliflozin lowers the risk of worsening heart failure and cardiovascular related death by 26 percent in patients with pre-existing heart failure with a low ejection fraction, when compared to placebo; regardless if the patient has diabetes or not.[14] The positive

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results of the DAPA-HF trial allowed for the dapagliflozin (Farxiga - AstraZeneca) to be the first SGLT2i to be approved by the US Food and Drug Administration (FDA) for use in nondiabetic heart failure patients with reduced ejection fraction.[15] Along with this, a recent study found that canagliflozin and empagliflozin showed a larger reduction in heart failure risk than other drugs for type 2 diabetes.[16] SGLT2i drugs are believed to be useful in the setting of heart failure due to it being a diuretic and the resulting volume reduction; however, there is still more research to be done to see the other effects these drugs have in the setting of heart failure. More trials looking at the effects SGLT2i on the cardiovascular system are currently underway, to DELIVER trial with results available in 2021 is assessing at dapagliflozin's effects on patients with heart failure but preserved ejection fraction.[1,17]

Kidney disease

Dapagliflozin has shown beneficial effects on the renal system, with studies suggesting that it has a role in decreasing hyperfiltration, albuminuria, and tubular injury in both diabetic and non-diabetic patients. SGLT2i cause natriuresis and increased sodium delivered to the macula densa activates tubuloglomerular feedback which results in intraglomerular pressure reduction due to constriction of the afferent arteriole, and decrease in the glomerular filtration rate. Studies have shown that these drugs are associated with decreased urinary proximal tubular injury biomarkers and reduction in inflammation and fibrosis formation, further suggesting its direct effects on the kidney.[18] This has led to the approval of SGLT2i worldwide for the expanded indication of reducing risk for end-stage renal disease in diabetic patients with chronic kidney disease.[15]

There is also promise with the combination therapy of renin angiotensin system (RAS) blockers and SGLT2i in non-diabetic patients with proteinuria, as RAS blocker therapy can be insufficient in many patients, leading to worsening kidney function - as there would be a reduction of the glomerular filtration rate, and subsequent inhibition of the RAS.[19] In current non-diabetic rat and mice models, results have been seen to vary. Other theories regarding the renoprotective effects of SGLT2i are attributed to a decrease in blood pressure, weight loss, and glycaemic control. Clinical trials are required to determine if the renal benefits of dapagliflozin are independent from the antihyperglycaemic effects.[18] One trial was stopped earlier, in March 2020 by AstraZeneca; The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) Phase III trial for dapagliflozin in patients with chronic kidney disease (CKD) with and without Diabetes type 2 demonstrated overwhelming efficacy and benefits earlier than originally anticipated.

Obesity

These drugs may have a role to play potentially as obesity treatment independent of diabetes as well. When used alone, the glucose/calorie loss in the urine is not enough to off-set food intake and yield significant weight loss. However, a number of studies have shown that when SGLT2i are taken adjuvantly with other agents that reduce appetite, there is a greater reduction in body weight. GLP1-RA coupled with SGLT2i have demonstrated moderate weight loss in the range of 4.5-5.7kg in patients without diabetes.[20] A clinical trial also showed meaningful reductions in body weight in obese non-diabetic patients when on canagliflozin and phentermine either in combination or each drug alone.[21]

Other benefits

SGLT2i may also have a unique role in the prevention of early stage, well-differentiated lung adenocarcinoma and precancerous lung lesions, as recent studies have shown SGLT2 expression and activity in these tumours. Canagliflozin was seen to have a role in increasing survival rates in mice by limiting glucose supply in these cells. Modified PET scans were used in the study to assess the activity of SGLT2, which has the potential to be useful in diagnosis of early lung cancers. However, the study had limitations concerning the fact that the therapeutic effects of canagliflozin were reversible due to upregulation of SGLT2. Along with this, the results of the study cannot be attributed to the knockout of SGLT2 in the cancer alone, and survival rates can be due to lowering of blood glucose rather than the inhibition of glucose uptake in the tumour.[22]

Adverse effects

SGLT2i may cause the following adverse effects, although rare. There is an increased risk of genital tract infections and lower limb amputation with the use of SGLT2i. Genital tract infections are seen twice as many times in patients taking SGLT2i when compared to placebo groups, but many of these cases were seen to be manageable.[7] The CANVAS trial found that canagliflozin increased the risk of lower limb amputation by 97%; however, empagliflozin had no such associations.[1] Volume depletion may contribute to decreased circulation in the distal artery beds, leading to increased risk for amputation. Genitourinary infections may occur due to glycosuria, warm/moist environment and decreased immunity in diabetics (mild/moderate infections); however, most patients did not require the need to discontinue medicines and were manageable.[1] Patients with lowered eGFR (<30 mL/min/1.73m^2) should not be started on these drugs, and if eGFR declines, then

Table-2: Available SGLT2i in Pakistan.

SGLT2i licensed for use in Pakistan	
Formulation and dose	**Frequency**
Dapagliflozin 5mg	Once a day
Dapagliflozin 10mg	Once a day
Dapagliflozin 5mg in combination with metformin 850mg	Twice a day
Dapagliflozin 5mg in combination with metformin 1000mg	Twice a day
Empagliflozin 10mg	Once a day
Empagliflozin 25mg	Once a day
Empagliflozin 12.5mg in combination with metformin 500mg	Twice a day
Empagliflozin 12.5mg in combination with metformin 850mg	Twice a day
Empagliflozin 12.5mg in combination with metformin 1000mg	Twice a day

therapy should be discontinued as the efficacy and safety of empagliflozin have not been established in patients with severe renal impairment.

Conclusion

SGLT2i uniquely reduces glucose reabsorption in the proximal convoluted tubules of the kidney resulting in glycosuria and natriuresis. The indications for their use continue to expand rapidly from patients with diabetes to heart failure and CKD, with others likely to be added in the future.

References

1. Simes BC, Mac Gregor GG. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Clinician's Guide. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2019.
2. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, et al. Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus (1). J Med Chem. 2010;53:6355-60
3. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: Characterisation and comparison with other SGLT-2 inhibitors. Diabetes, Obes Metab. 2012;14:83-90
4. Johnson EL, Feldman H, Butts A, Billy CDR, Dugan J, Leal S, et al. Standards of medical care in diabetes—2019 abridged for primary care providers. Clin Diabetes. 2019;37: 11-34
5. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials. Diabetes, Obes Metab. 2014;16:457-466
6. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes, Obes Metab. 2016;18:783-94
7. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: Rationale and clinical prospects. Nature Reviews Endocrinology. 2012;8:495-502
8. Mogensen CE. Maximum tubular reabsorption capacity for glucose and renal hemodynamics during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest. 1971;28:101-109
9. Europe embraces, FDA rejects use of SGLT inhibitors for type 1 diabetes [Internet]. [cited 2020 Jul 12]. Available from: https://www.healio.com/news/endocrinology/20190723/europe-embraces-fda-rejects-use-of-sglt-inhibitors-for-type-1-diabetes
10. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, Von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375:323-34
11. 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;373:2117-28
12. 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; 380:347-357
13. Giugliano D, Esposito K. Class effect for SGLT-2 inhibitors: A tale of 9 drugs. Cardiovasc. Diabetol. 2019:18:94
14. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381:1995-2008
15. Farxiga approved in the US for the treatment of heart failure in patients with heart failure with reduced ejection fraction [Internet]. [cited 2020 Jul 12]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-approved-in-the-us-for-the-treatment-of-heart-failure-in-patients-with-heart-failure-with-reduced-ejection-fraction.html
16. Kramer CK, Ye C, Campbell S, Retnakaran R. Comparison of New Glucose-Lowering Drugs on Risk of Heart Failure in Type 2 Diabetes: A Network Meta-Analysis. JACC Hear Fail [Internet]. 2018 Oct 1 [cited 2020 Jul 12];6(10):823–30. Available from: https://pubmed.ncbi.nlm.nih.gov/30196071/
17. Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure. - Full Text View - ClinicalTrials.gov [Internet]. [cited 2020 Jul 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT03619213?term=dapagliflozin&cond=heart+failure+with+preserved+ejection+fraction&rank=1
18. Vergara A, Jacobs-Cachá C, Soler MJ. Sodium-glucose cotransporter inhibitors: Beyond glycaemic control. Clin Kidney J. 2019;12:322-325
19. Perico N, Ruggenenti P, Remuzzi G. ACE and SGLT2 inhibitors: the future for non-diabetic and diabetic proteinuric renal disease. Curr Opin Pharmacol. 2017;33:34-40
20. Lundkvist P, Pereira MJ, Katsogiannos P, Sjöström CD, Johnsson E, Eriksson JW. Dapagliflozin once daily plus exenatide once weekly in obese adults without diabetes: Sustained reductions in body weight, glycaemia and blood pressure over 1 year. Diabetes, Obes Metab. 2017; 19:1276-1288
21. Hollander P, Bays HE, Rosenstock J, Frustaci ME, Fung A, Vercruysse F, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: A randomized clinical trial. In: Diabetes Care. 2017;40:632-639
22. Scafoglio CR, Villegas B, Abdelhady G, Bailey ST, Liu J, Shirali AS, et al. Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. Sci Transl Med. 2018;10: eaat5933 doi: 10.1126/scitranslmed.aat5933.