Role of Dapagliflozin in Diabetic and Non-Diabetic Heart Failure

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Abstract

Background

Selective sodium-glucose cotransporter-2 (SGLT-2) has been known for years to be effective in the management of hyperglycaemia in diabetic patients. It results in moderate reduction in HbA1C levels, weight and blood pressure in diabetic patients. Recently, it has become apparent that they have a role in management of patients with heart failure with or without diabetes.

Objective

A review of recent literature has been carried out to establish the most current and up-to-date evidence to ascertain their effectiveness and safety. Dapaglifozin has been chosen as the drug to be reviewed, due to its recent approval from FDA for diabetic and non-diabetic heart failure.

Method

Sources such as pubmed central, google-scholar, research gate and the cochrane library have been consulted from 1998 till 31st August 2020 to study data from randomised control trials of Dapagliflozin and SGLT-2, and its effect on heart failure in individuals with or without diabetes. In particular, we looked for evidence for cardiovascular outcome, and additionally we looked at the renal outcome and drug safety profile.

Results

Dapagliflozin has shown significant benefit in cardiovascular outcome in patients with heart failure, in both with or without diabetes. It has shown a marked reduction in hospitalisation, urgent appointments and cardiac death in patients with heart failure. Furthermore, it has demonstrated a reduction in progression of renal disease.

Conclusion

Dapagliflozin shows efficacy and safety in individuals with heart failure. It has recently been approved by FDA for heart failure, which underlines the potential for the use of other SGLT-2 inhibitors in heart failure management. This may indicate changes in the heart failure guidelines accordingly.

Introduction

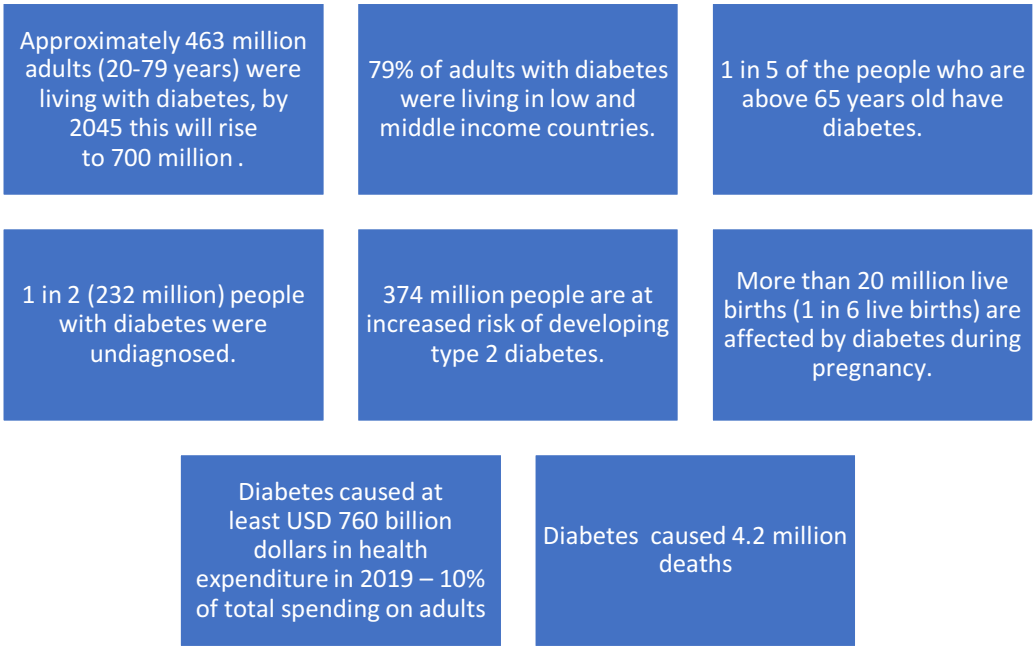
Diabetes is a chronic condition in which the pancreas cannot produce insulin or when there is resistance in the body to make good use of the insulin that is produced. Insulin is a hormone produced by the pancreas which facilitates the transport of glucose in the blood, from the food we eat to be utilised at cellular level as energy source. Hence in the absence of insulin or having insulin resistance causes hyperglycaemia. The long-term consequnces of hyperglycaemia include damage to various body organs and tissue (1).

There are three main types of diabetes – Type 1, Type 2 and Others

- **Type 1 diabetes** is when the body produces very little or no insulin. Type 1 diabetes can develop at any age, but most frequently affects children or adolescents and is managed administering insulin, most commonly via subcutaneous injection (2).
- **Type 2 diabetes** is when the body develops resistance to the Insulin produced. It is more common in adults, and accounts for around 90% of all diabetes (2). Lifestyle interventions such as weight loss and physical exercise play a key role in the management of type 2 diabetes. The vast majority of patients require oral medication to manage their condition and over time a significant proportion require insulin (2).
- **Others**
    - **Gestational diabetes (GDM)** consists of hyperglycaemia during pregnancy and is associated with complications in both the mother and baby. GDM usually resolves after pregnancy but women and the children both are at higher risk of developing type 2 diabetes later in life (2).

- **Maturity onset diabetes of young (MODY)** is an inherited condition, and results from a single gene mutation in the parent. It is an autosomal dominant condition and hence there is 50% chance of any child of the parent with mutated gene to inherit it. The child with the mutated gene usually develops MODY before the age of 25 years (3).
- **Latent autoimmune diabetes in adult (LADA)** is currently not been classed as a separate form of diabetes. It sorts of sits somewhere in the middle of Type-1 and Type-2 diabetes, hence is sometimes called type-1.5 diabetes. Further research is required to understand how to differentiate LADA from Type 1 and Type 2 diabetes (4).

International Diabetes Federation (IDF) facts and figures have shown the prevalence of diabetes as below in 2019:



Adapted from International Diabetes Federation (IDF) 2019

Literature Review

What are SGLT-2 inhibitors? Their mechanism of action and role in T2DM:

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a fairly new class of oral hypoglycaemic agents (OHA). They have been developed based on the discovery of phlorizin, which is a natural product which inhibits SGLT activity. It was extracted from the bark of the apple tree in 1835, since then with the advancements has caused us to identify SGLTs, and their properties in glucose transport in 1980-1990 (11).

SGLT-2 inhibitors are absorbed from the gut rapidly and they have a long half-life, hence requiring once daily dose. They are metabolised in liver through process of glucuronidation to inactive metabolites. The parent drug has very low excretion though kidneys. Furthermore, it is not known to have clinically significant drug–to- drug interaction (12).

Human kidney filters 180g of glucose through a glomerular filtration process. SGLT-1 and SGLT-2 are present in proximal tubules, and they absorb almost all the filtered glucose load and ensuing glucose is not excreted in urine. Basolateral sodium/potassium-ATPase causes active extrusion of sodium and glucose uptake by the cell from the tubules against intracellular uphill gradient. Once inside the cell, glucose is transported out of the cell basolaterally via glucose transporter-2 (GLUT2) (6). 90% of filtered glucose is reabsorbed in proximal tubules mainly in segment 1 and 2 by SGLT-2, while the remaining glucose is reabsorbed in proximal tubules segment 3 by SGLT-1. In the event of hyperglycaemia, the glucose reabsorption increases to by 30%, although it is not known if this is due to increased expression of SGLT-2 in diabetic patients. In animal experiments, it has shown that by knocking SGLT-2, the SGLT-1 has compensated and hence increasing its absorption up to 35% of the filtered glucose load (6)(12)(13) Figure 1-2.

A and B: Glucose reabsorption via SGLT1 and SGLT2 in normal and diabetic kidney

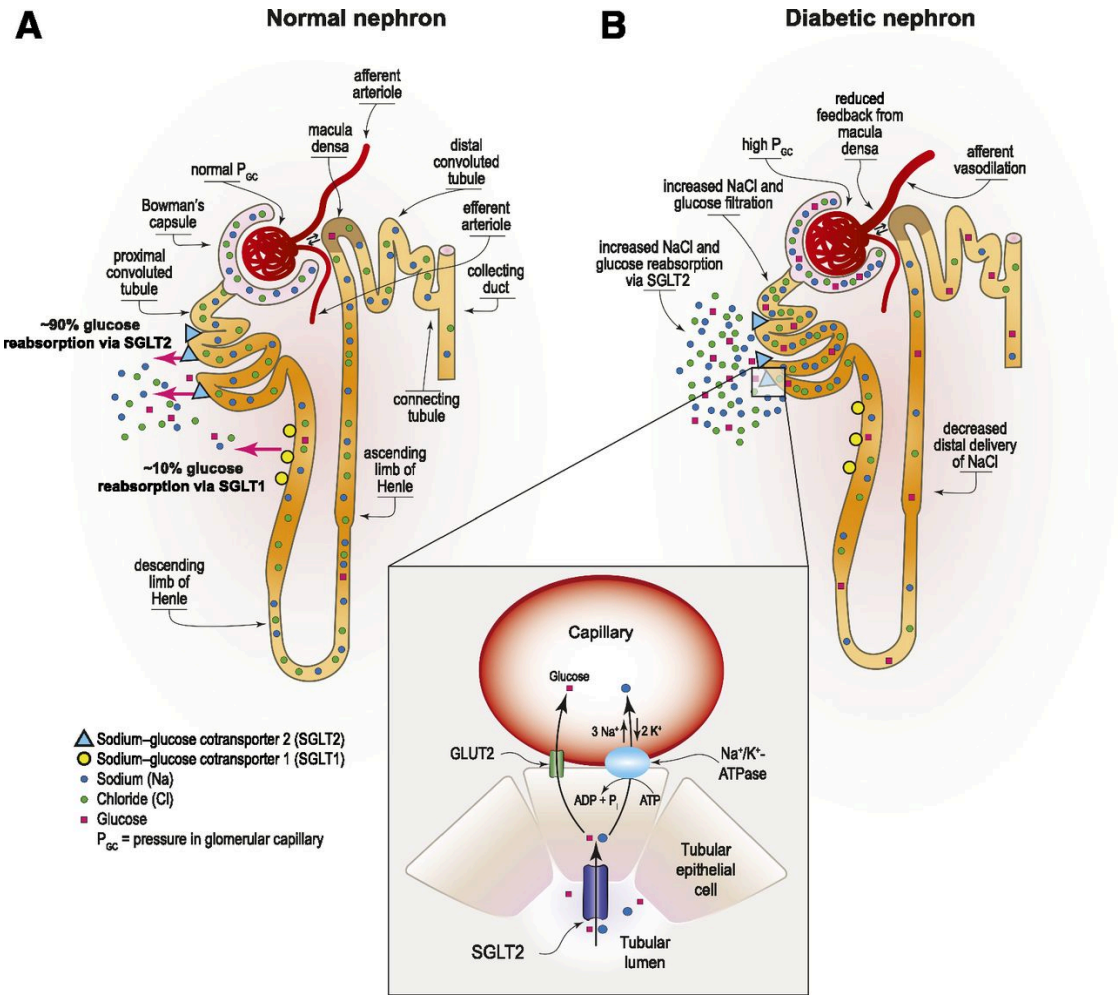


Figure-1 Taken from diabetesjournals.org (13)

A *and* B*: Glucose reabsorption via SGLT1 and SGLT2 in normal and diabetic kidney. Expressed apically in the epithelium of the proximal convoluted tubule, SGLT2 reabsorbs about 90% of glucose from the urinary filtrate. The remaining 10% is reabsorbed by SGLT1, a high-affinity and low-capacity transporter expressed apically in the epithelium of the straight descending proximal tubule.*

Effects of diabetes and SGLT2 inhibition on nephron hemodynamics

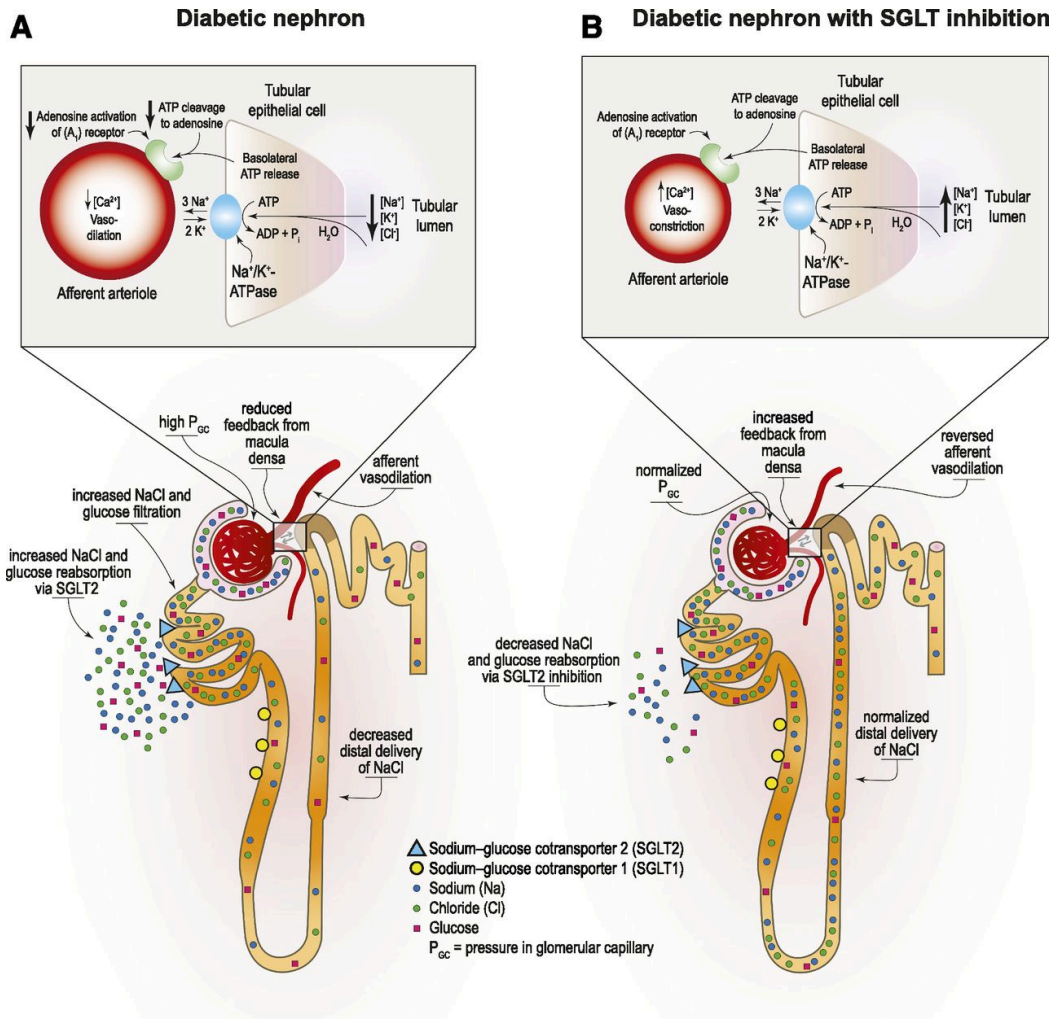


Figure-2 Taken from diabetesjournals.org (13)

Effects of diabetes and SGLT2 inhibition on nephron hemodynamics. A*: Increased reabsorption of glucose by SGLT2 in the proximal convoluted tubule decreases delivery of solutes to the macula densa. The resulting decrease in ATP release from the basolateral membrane of tubular epithelial cells reduces production of adenosine and produces a vasodilatation of the afferent arteriole.* B*: SGLT2 inhibitors restore solute delivery to the macula densa with resulting adenosine activation and reversal of vasodilation of the afferent arteriole.*

Dapagliflozin blocks reabsorption of glucose by inhibition of SGLT-2, as a result, the filtered glucose is not reabsorbed into proximal tubules segment 1 and 2, thus increasing the urinary glucose excretion by approximately 60–80g/day and hence improving hyperglycaemia. This excretion of 60–80g of excess glucose corresponds to the loss of up to 320 kcal from the body which results in weight loss. The weight loss in turn helps to improve obesity and reduce abdominal fat which causes improvement in the insulin resistance and metabolic parameters such as lipid profile, blood pressure and serum uric acid level (10) (Figure-3). SGLT-2 inhibitor monotherapy does not increase the risk of hypoglycaemia (14).

SGLT-2 like Dapagliflozin are a newer class of medication, and further clinical studies are needed to understand their long-term safety and side effects. The most common problem reported is genital mycotic infection that respond to the standard antifungal treatment. In RCT trials, this adverse effect seldom required to discontinue treatment. The data available for potential risk of UTI in such patients is not clear as some trials have suggested increase in UTIs, while other trials have shown no increased risk compared to the control group. The risk of euglycemic ketoacidosis is low provided that a reasonable intake of carbohydrates and water is maintained (13).

Mechanism of action of SGLT-2 inhibitor

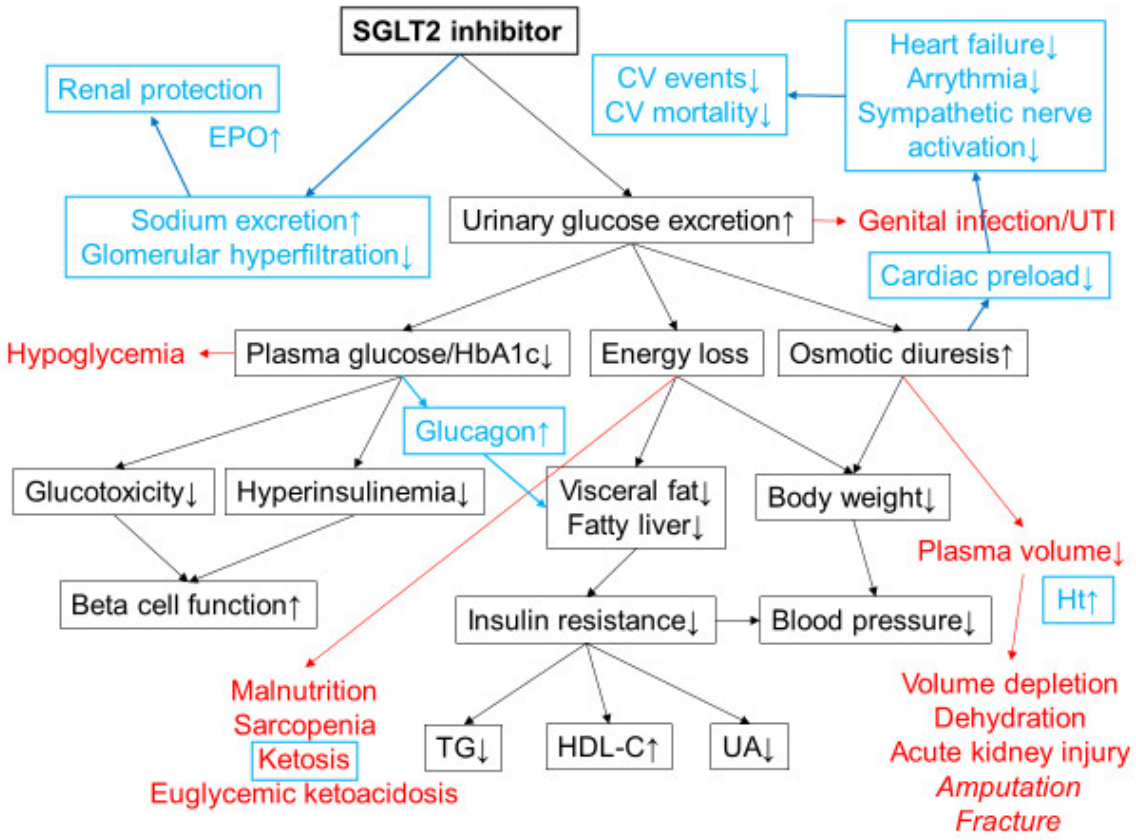


Figure-3- (11)

SGLT2 inhibitors lower plasma glucose level by increasing urinary glucose excretion. Energy loss by SGLT2 inhibitor treatment promotes weight loss and improves insulin resistance and various metabolic parameters. Possible adverse effects are shown in red. Increased risk of lower-extremity amputation and bone fracture has been reported in a clinical trial with canagliflozin. The cardiorenal benefits shown in CVOTs have revealed additional mechanisms of action of SGLT2 inhibitors that were unknown at the time of launch (highlighted in blue). Osmotic diuresis and natriuresis are likely to be the major mechanisms of the cardiorenal benefits of SGLT2 inhibitors. Increases in blood ketone bodies and hematocrit may also contribute to the cardiorenal benefits. CV; cardiovascular, TG; triacylglycerol, HDL-C; high density lipoprotein cholesterol, UA; uric acid, Ht; hematocrit, UTI; urinary tract infection, EPO; erythropoietin

Beneficial effects of Dapagliflozin in T2DM in general and with Heart Failure

Dapagliflozin is a selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor. It is a very potent inhibitor of SGLT-2 and is reversible in its action(5). Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a fairly new class of antidiabetic for the treatment of type 2 diabetes (6)(7). They act by reducing the reabsorption of glucose in the kidneys and facilitate its excretion in the urine by inhibiting the high-capacity glucose transporter SGLT2 located in the proximal convoluted tubule, thereby reducing glucose levels independently of insulin action (5)(6). Hence Dapagliflozin complements the action when used with other anti-diabetic medication. Dapagliflozin increases the amount of glucose excreted in the urine and hence it improves both fasting and post-prandial plasma glucose levels in patients with type 2 diabetes(8).

Furthermore, research has shown that Dapagliflozin has reduced the rate of cardiovascular (CV) deaths or hospitalization form heart failure (HHF) and possibly reduced progression of renal disease relative to placebo in patients with established atherosclerotic CV disease (CVD) or multiple risk factors for CVD(5).

The DECLARE–TIMI 58 trial was a randomized, double-blind, multinational, placebo-controlled, phase 3 trial of Dapagliflozin in type 2 diabetic patients who had risk factors for atherosclerotic cardiovascular disease or had established cardiovascular disease. Results have shown that Dapagliflozin was non-inferior compared to placebo, in patients type 2 diabetes considering the safety outcome of major adverse cardiovascular events (MACE) i.e. cardiovascular death, myocardial infarction or ischemic stroke. Also, it has also shown that Dapagliflozin has not caused lower rates for those who are at higher risk for MACE compared to placebo. The interesting finding of the trial was that Dapagliflozin has shown lower rate of cardiovascular death or hospitalization for heart failure compared to placebo, and in addition it has shown a possible lower rate of adverse renal outcomes (9)(10).

Therapeutic effect in diabetes and cardiovascular risk factor

Patients with diabetes are at higher risk of developing atherosclerotic cardiovascular disease(15)(16), renal disease(17) and heart failure(18). This increased risk of heart failure in patients with diabetes is independent of coronary artery disease. Currently, there is insufficient data to guide treatments for the prevention of heart failure in such patients (19)(20). Hence it is vital to determine the therapies for diabetes, which in addition to improve glycaemic control, are not only safe but help to reduce the cardiovascular risk (21)(22).

DECLARE–TIMI 58 was a large trial that evaluated cardiovascular outcomes with the SGLT-2 inhibitor, dapagliflozin. Over 17,000 patients were monitored for a median of 4.2 years including around 10,000 patients without apparent atherosclerotic cardiovascular disease. Prior to this trial, the data on the effects of SGLT-2 inhibitors on this cohort of patients was lacking (9).

On the basis of results from previous trials(21)(23)(24), current international guidelines for the management of diabetes have focused on the use of SGLT-2 inhibitors in patients with atherosclerotic cardiovascular disease. The results from DECLARE-TIMI 58 trial have shown that dapagliflozin was non-inferior compared to placebo, in patients type 2 diabetes considering the safety outcome of major adverse cardiovascular events (MACE) i.e. cardiovascular death, myocardial infarction or ischemic stroke. Furthermore, it has also shown that dapagliflozin has not resulted in lowering the rates of those who are at higher risk for MACE compared to placebo. As mentioned earlier, the remarkable finding of the trail was that dapagliflozin has shown a lower rate of cardiovascular death or hospitalization for the heart failure compared to placebo (9)(10).

This lower rate of hospitalization and cardiovascular death for heart failure in the dapagliflozin was consistent in multiple groups. Hence dapagliflozin has resulted in preventing cardiovascular events, mainly hospitalisation for heart failure and this is irrespective of a history of atherosclerotic cardiovascular disease or heart failure. Similarly, Dapagliflozin has shown lower rates of progression of renal disease among patients with and without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease at baseline (9).

Cardiovascular outcome in non-diabetic heart failure:

As discussed previously, SGLT-2 inhibitors have been shown to reduce the risk of cardiovascular events mainly by decreasing the risk of development or progression of heart failure and hence causing reduction in hospitalisation for heart failure (9). These results were observed very early after randomization, creating scope for further trials to understand the mechanism of action of dapagliflozin, which is different from the glucose lowering effect (25).

The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial is a prospective study to assess the efficacy and safety of the SGLT2 inhibitor, dapagliflozin, in patients with heart failure and a reduced ejection fraction (HFrEF). The study included 4,744 patients with HFrEF who were investigated for the effect of dapagliflozin (10mg daily) for a median of 1.52 years. This included patients with diabetes mellitus diagnosis (41.8%), and without diabetes mellitus diagnosis

(58.2%). Patients who were included had an ejection fraction of ≤ 40% and New York Heart Association (NYHA) class II, III, or IV symptoms (26).

The primary outcome that was monitored was composite worsening of heart failure or death from cardiovascular causes as well as unplanned hospitalisation or visit regarding urgent heart failure therapy. The trial showed an improvement in the 55% of patients who did not have diagnosis of type 2 diabetes compared to those who have diagnosis of diabetes.

It has been observed in all pre-specified sub-groups that the primary outcome risk was reduced. Hence, patients with HFrEF who received dapagliflozin had reduced risk of worsening of heart failure or death from cardiovascular cause, and have shown improvement in symptoms compared to the placebo group (26).

In an analysis of DAPA-HF trial, patients were examined with the effects of dapagliflozin in HFrEF patient measuring symptoms control, physical function and quality of life using Kansas City Cardiomyopathy Questionnaire (KCCQ), which has indicated that patients did indeed experience improvement in their health status, whether small, moderate or large(26).

It is hypothesised that the cardiovascular effect of dapagliflozin is due to a mechanism of action other than the effect to improve hyperglycaemia. In addition to the diuretic effect, it has been proposed that there may be changes which affect myocardial metabolism, fibrosis, ion transport, adipokines and vascular function.(27) (28)(29).

DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in patients with HF with Reduced Ejection Fraction) is a double blinded, randomized and placebo-controlled trial, investigating the effects of dapagliflozin in HFrEF patients with left ventricular ejection fraction (≤40%). Dapagliflozin has demonstrated a safety profile as observed in the previous studies. It was well tolerated, and only a minimal number of patients have stopped medication due to any adverse effects. This was the first rigorous study which has shown the effect of drug tolerance in patients with HFrEF without diabetes. The results have shown that use of dapagliflozin over 12 weeks has resulted in significant improvement in patient's experience of heart failure symptoms with or without diabetes. However, it did not affect the mean NT-proBNP (30).

Discussion

The purpose of the literature review was to study the recent evidence of SGLT-2 in view of their effect on patients with heart failure with or without diagnosis of diabetes. Dapagliflozin (SGLT-2) has shown significant reduction in cardiovascular related deaths and hospitalisation in patients with heart failure with diabetes, despite the fact that their effect on long-term glycaemic control is modest. Furthermore, a significant decline is observed in a similar group of patients in end-stage renal disease. In diabetic patient treatment with SGLT-2 like dapagliflozin, causes a 1% reduction in HBA1C with added benefit of arterial blood pressure and weight (31).

The trial carried out for the effect of Dapagliflozin in diabetic patients have raised the possibility of a mechanism of action other than their glucose lowering effect, to be responsible for the cardiac and renal outcomes in patients with and without diabetes. These multiple non-glycaemic benefits of dapagliflozin have made it favourable in the treatment of diabetic patients with heart failure. As the results were seen quite early in the randomisation, thus the question was raised about dapagliflozin being beneficial in heart failure without diabetes. In view of the strength of evidence gained in the DECLARE-TIMI 58 trial, dapagliflozin has gained approval from FDA in 2019 for patients with type 2 diabetes and multiple cardiovascular risk factors, or established cardiac disease(32).

Patients with diabetes are twice as likely to develop chronic kidney disease and are six times more likely to develop end stage kidney disease. In the DECLARE-TIMI 58 trial, dapagliflozin has shown significant reduction in progressive renal failure and renal death (33).

In a double blinded, randomised, placebo-controlled trial carried out on patients with HFrEF without diabetes has later shown significant improvement with dapagliflozin. There was significant reduction in urgent visits related to heart failure, hospitalisation for heart failure and cardiovascular deaths compared to the control group. The exact mechanism of action by which dapagliflozin improves the cardiovascular outcome in HFrEF is not yet known. It is hypothesised that it is multifactorial as a result of diuretic effect and by influencing myocardial metabolism, fibrosis, ion transport, adipokines and vascular function.

To establish the exact mechanism of action by which the improvement in cadiovacular outcome in HFrEF is achieved would need further studies. Accepting the results from clinical trials, FDA has recently approved dapagliflozin for heart failure with reduced ejection fraction (HFrEF) in adults with and without type 2 diabetes (T2D). As such, for the first time, a medication which was approved for diabetes was approved for heart failure even in the absence of diabetes(34).

The most commonly reported adverse effects of dapagliflozin are mycotic genital infections both in men and women, which were twice as often in women than men. Most infections are of a mild nature, and respond to usual antifungal treatment. Other common adverse effects reported are volume depletion, UTIs, hypoglycemia (if given with insulin or insulin secretogogue). Less common side effects are acute kidney injury, diabetic ketoacidosis, bladder cancer, lower limb amputation, bone fracture and Fournier's gangrene (13). We have not discussed the adverse effects in detail here as this is not within the scope of this review.

Adverse Effects of SGLT-2 Inhibitor

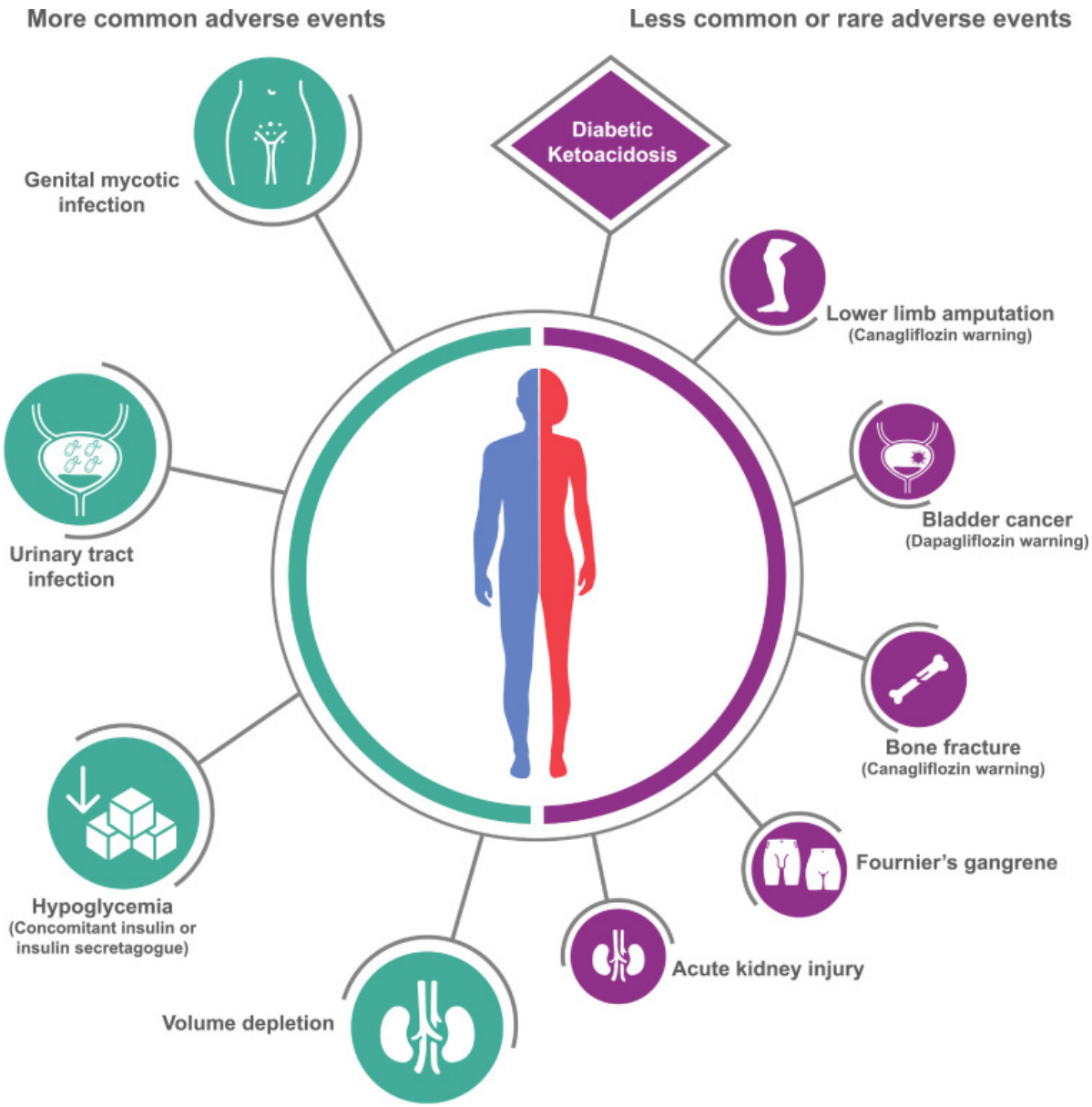


Figure-2 (14)
Summary of adverse events potentially associated with sodium-glucose co-transporter 2 inhibitors

Conclusion

Dapagliflozin is a well known SGLT-2 that has been successfully used in the management of diabetes type 2 for many years. It has a fairly established safety profile and has minimal side effects. There is strong evidence suggesting an improvement in cardiovascular outcome in patients with heart failure in patients with diabetes. Last year, it was approved by FDA for management of heart failure in type 2 diabetes with cardiovascular risk factors or established atherosclerotic cardiovascular disease.

With the recent FDA approval, dapagliflozin now holds a very strong position in the management of heart failure (HFrEF), particularly in view of the evidence from the trial suggesting reduction in heart failure related death, urgent visits and hospitalisation with or without diabetes. This has created an opportunity to explore the potential of other SGLT-2 in the treatment of heart failure. In addition, trials have also shown a strong association with protection from a serious decline in renal function.

Reference

1. International Diabetes Federation - Facts & figures [Internet]. [cited 2020 Aug 31]. Available from: https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html

2. International Diabetes Federation - What is diabetes [Internet]. [cited 2020 Aug 31]. Available from: https://www.idf.org/aboutdiabetes/what-is-diabetes.html

3. Maturity onset diabetes of the young (MODY) | Diabetes UK [Internet]. [cited 2020 Aug 31]. Available from: https://www.diabetes.org.uk/diabetes-the-basics/other-types-of-diabetes/mody

4. Latent Autoimmune Diabetes in Adults (LADA) | Diabetes UK [Internet]. [cited 2020 Aug 31]. Available from: https://www.diabetes.org.uk/diabetes-the-basics/other-types-of-diabetes/latent-autoimmune-diabetes

5. (PDF) Dapagliflozin: A Review in Type 2 Diabetes [Internet]. [cited 2020 Aug 31]. Available from: https://www.researchgate.net/publication/334010617_Dapagliflozin_A_Review_in_Type_2_Diabetes

6. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):73–9.

7. Wilding J, Fernando K, Milne N, Evans M, Ali A, Bain S, et al. SGLT2 Inhibitors in Type 2 Diabetes Management: Key Evidence and Implications for Clinical Practice. Diabetes Ther Res Treat Educ Diabetes Relat Disord. 2018 Oct;9(5):1757–73.

8. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. Clin Pharmacol Ther. 2009 May;85(5):513–9.

9. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes | NEJM [Internet]. [cited 2020 Aug 31]. Available from: https://www.nejm.org/doi/10.1056/NEJMoa1812389?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

10. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) | Diabetes Care [Internet]. [cited 2020 Aug 31]. Available from: https://care.diabetesjournals.org/content/43/2/487.long

11. (PDF) SGLT2 Inhibitors: the Star in the Treatment of Type 2 Diabetes? [Internet]. ResearchGate. [cited 2020 Aug 31]. Available from: https://www.researchgate.net/publication/341300110_SGLT2_Inhibitors_the_Star_in_the_Treatment_of_Type_2_Diabetes

12. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015 Jan;75(1):33–59.

13. Sodium–Glucose Cotransporter 2 Inhibition and Diabetic Kidney Disease | Diabetes [Internet]. [cited 2020 Sep 1]. Available from: https://diabetes.diabetesjournals.org/content/68/2/248

14. McGill JB, Subramanian S. Safety of Sodium-Glucose Co-Transporter 2 Inhibitors. Am J Cardiol. 2019 Dec 15;124:S45–52.

15. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart Disease and Stroke Statistics—2011 Update. Circulation. 2011 Feb 1;123(4):e18–209.

16. Diabetes and Mortality Following Acute Coronary Syndromes | Acute Coronary Syndromes | JAMA | JAMA Network [Internet]. [cited 2020 Aug 31]. Available from: https://jamanetwork.com/journals/jama/fullarticle/208441

17. Nephropathy in Patients with Type 2 Diabetes Mellitus | NEJM [Internet]. [cited 2020 Aug 31]. Available from: https://www.nejm.org/doi/10.1056/NEJM199910073411506?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

18. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, Obesity, Diabetes, and Heart Failure-Free Survival: The Cardiovascular Disease Lifetime Risk Pooling Project. JACC Heart Fail. 2016;4(12):911–9.

19. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America | Circulation [Internet]. [cited 2020 Aug 31]. Available from: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000509

20. 2013 ACCF/AHA Guideline for the Management of Heart Failure. :88.

21. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2018 | Diabetes Care [Internet]. [cited 2020 Aug 31]. Available from: https://care.diabetesjournals.org/content/41/Supplement_1/S86

22. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2018 | Diabetes Care [Internet]. [cited 2020 Aug 31]. Available from: https://care.diabetesjournals.org/content/41/Supplement_1/S73

23. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2018 | Diabetes Care [Internet]. [cited 2020 Sep 1]. Available from: https://care.diabetesjournals.org/content/41/Supplement_1/S86

24. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure | European Heart Journal | Oxford Academic [Internet]. [cited 2020 Sep 1]. Available from: https://academic.oup.com/eurheartj/article/37/27/2129/1748921

25. Report from the 5th cardiovascular outcome trial (CVOT) summit | Cardiovascular Diabetology | Full Text [Internet]. [cited 2020 Sep 1]. Available from: https://cardiab.biomedcentral.com/articles/10.1186/s12933-020-01022-7#ref-CR22

26. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction | Circulation [Internet]. [cited 2020 Sep 1]. Available from: https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.119.044138

27. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure | Circulation [Internet]. [cited 2020 Sep 1]. Available from: https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.117.030012

28. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review | SpringerLink [Internet]. [cited 2020 Sep 1]. Available from: https://link.springer.com/article/10.1007/s00125-018-4670-7

29. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction | NEJM [Internet]. [cited 2020 Sep 1]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1911303

30. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction | Circulation [Internet]. [cited 2020 Sep 1]. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.042929

31. Anderson SL. Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf. 2014 Dec;5(6):242–54.

32. FDA Approves Farxiga to Reduce HF Hospitalization Risk in CVD, Diabetes Patients - American College of Cardiology [Internet]. [cited 2020 Sep 1]. Available from: https://www.acc.org/latest-in-cardiology/articles/2019/10/21/17/04/fda-approves-farxiga-to-reduce-hf-hospitalization-risk-in-cvd-diabetes-patients

33. DECLARE Shows Diabetes Drug Farxiga Prevented Renal Decline, Even for Those With Good Kidney Health | AJMC [Internet]. [cited 2020 Sep 1]. Available from: https://www.ajmc.com/view/declare-shows-diabetes-drug-farxiga-prevented-renal-decline-even-for-those-with-good-kidney-health

34. FDA Approves Dapagliflozin to Treat Heart Failure, Breaking New Ground in SGLT2 Competition | AJMC [Internet]. [cited 2020 Sep 1]. Available from: https://www.ajmc.com/view/fda-approves-dapagliflozin-to-treat-heart-failure-breaking-new-ground-in-sglt2-competition