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The Use of SGLT2 Inhibitor, Empagliflozin, to Reduce Cardiovascular Risk in Type 2 Diabetes Mellitus Patients

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PERMISSION

Title The Use of SGLT2 Inhibitor, Empagliflozin, to Reduce Cardiovascular Risk in Type 2 Diabetes Mellitus Patients.

Department Nursing

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Abstract

Type 2 diabetes mellitus is a major risk factor for cardiovascular disease. The likelihood of mortality significantly increases when type 2 diabetes mellitus and cardiovascular disease coincide (Zinman et al., 2015). Consequently, cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus. Reducing cardiovascular risk is essential in successful management of diabetes. In 2015, the EMPA-REG OUTCOME trial demonstrated that the SLGT2 inhibitor, empagliflozin, provided significant cardiovascular benefits, among other protective effects, beyond simply lowering blood glucose levels (Naing, Poliyedath, Khandelwal & Sigala, 2016). This independent study aims to address the effects empagliflozin has on improving cardiovascular mortality and morbidity in type 2 diabetes mellitus patients.

Keywords: type 2 diabetes mellitus, empagliflozin, cardiovascular disease

Background

Type 2 diabetes mellitus is a chronic disease that requires long term medical treatment and monitoring to effectively limit the devastating progression of the disease process. The effects type 2 diabetes mellitus has on the cardiovascular system have been extensively researched, proving patients are at an increased risk for myocardial infarction, stroke, and heart failure. Cardiovascular disease accounts for an overwhelming percentage of mortality in patients with type 2 diabetes mellitus. Approximately two thirds of people with diabetes die of heart disease or stroke (Khardori, 2017).

Treatment goals for type 2 diabetes mellitus consists of lifestyle modifications including diet, exercise, smoking cessation, and pharmacotherapy (Dixit, Yoon, Volino, & Mansukhani, 2015). Although, there are many anti-hyperglycemic agents available, the following paper will specifically focus on the sodium glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin (Jardiance®).

SGLT2 inhibitors improve glycemic control by inhibiting reabsorption of glucose from the proximal tubules in the kidney, lowering the renal threshold for glucose, thus increasing urinary glucose excretion (Scott, 2014; Dixit et al., 2015; McGovern, Feher, Munro, & Lusignan, 2017). Since the mechanism of action of empagliflozin is not insulin-dependent, it may be used in patients with nonfunctional or impaired pancreatic beta cells and in combination with other antidiabetic agents given its low risk of hypoglycemic effects (Dixit et al., 2015).

In December 2016, the US Food and Drug Administration (FDA) approved empagliflozin (Jardiance ®) for the "new indication of improving survival in adults with type 2 diabetes and cardiovascular disease" (Tucker, 2016, para 1). The Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial was the first clinical trial to

demonstrate a significant reduction in cardiovascular effects with the use of an antidiabetic agent (McGovern et al., 2017; Simo & Hernandez, 2016).

This independent study aims to address the effects empagliflozin has on improving cardiovascular mortality and morbidity in type 2 diabetes mellitus patients. The foundation of this report is based on the case of a 60 year-old Caucasian female with a ten-year history of type 2 diabetes mellitus with a significant family history of cardiovascular disease.

Case Report

History

A 60-year-old Caucasian female presented to her primary care office for a diabetes follow-up. She was diagnosed with type II diabetes mellitus 10 years ago. Since diagnosis, she has maintained disease progression on 500 mg Metformin twice daily, along with lifestyle modifications, including diet and exercise. She was last seen in the clinic six months ago. Her hemoglobin A1C was 8.2% at that time. She was instructed to meet with a diabetes educator to aid in making healthy food choices and follow-up in six months. Today, she states she feels well and denies complaints. She monitors her blood glucose levels twice weekly, with results ranging from 150-200 mg/dL. She denies any hypoglycemic episodes. She reports strict compliance with her medications and denies medication side effects. Her typical diet includes: cereal for breakfast, fried chicken and French fries for lunch, a hamburger for supper, and numerous sweet treats for snacks throughout the day. She walks about two miles every day for exercise. She denies use of tobacco, illicit drugs, or alcohol. Her last eye exam was 3 months ago and she states she follows up on this annually.

Her past medical history includes hypertension (age of onset 42) and hyperlipidemia (age of onset 45). She has a significant family history including; heart disease in both of her parents.

Her mother died at the age of 80 from what she describes as a “silent” heart attack. Her father also passed away at age 89 from cardiac complications, specifics unknown.

Along with her diabetic medication, she is also taking 81 mg Aspirin daily, 20 mg Lisinopril daily, 20 mg Atorvastatin daily, and a multivitamin. She reports an allergy to penicillin.

Review of Systems and Physical Exam

The review of systems was grossly negative. She denies polyuria, polyphagia, polydipsia, weight loss or gain, fever, chills, sleep disturbance, nausea, diarrhea, constipation, headaches, numbness/tingling to bilateral extremities, weakness, dizziness, chest pain, or dyspnea. She does report ongoing fatigue for the last few months, however, this has not interfered with her activities of daily living.

Her vitals were as follows: blood pressure 148/98, heart rate 80, respirations 20, and temperature 98.6, BMI 27. Her physical exam was unremarkable. She was alert and oriented, well-groomed, well-nourished and in no acute distress. Lung fields were clear upon auscultation with a normal respiratory rate and rhythm. S1 and S2 were also auscultated without adventitious heart sounds, including murmurs, gallops or clicks. Her abdomen was soft, nontender, nondistended, with active bowel sounds in all four quadrants. No edema was present. Her diabetic foot exam revealed warm, dry, intact skin to bilateral feet, pulses were 2+ bilaterally, monofilament exam was 5/5 bilaterally, and no sores or calluses were noted.

Lab workup included a TSH for ongoing fatigue (results were within normal limits), a lipid panel, BMP, CBC, and Hemoglobin A1C. Her fasting lipid panel revealed elevated cholesterol at 209, triglycerides 184, HDL 31, and LDL 95. Her glucose was 96. BUN 9, serum

creatinine 0.8. Her CBC was grossly normal. The hemoglobin A1C increased from 8.2% 6 months ago, to 8.5% today.

Management of Care

In discussion with the patient, we opted to initiate a SGLT2 inhibitor, Jardiance 10 mg every morning, in addition to her metformin twice daily. She should continue to monitor her blood glucose levels two to three times a week and record those levels. Lifestyle modification was reinforced, including consuming a healthier, well-balanced, diabetic meal, and increasing her physical activity daily. Given her elevated blood pressure today, she was instructed to monitor her blood pressures at home daily for one week and call the clinic with those results. Her atorvastatin was increased to 40 mg daily to reduce her lipid levels, thus reducing risk for heart attacks and stroke. She was instructed to follow-up in the clinic in 3 months, including a recheck of her Hgb A1C, fasting lipid panel, and glucose levels.

Literature Review

The above case report represents a female patient at risk for developing cardiovascular disease. Although, she does not have a personal medical history of cardiac disease, her significant family history and a number of other risk factors increase her risk for developing cardiovascular disease, including hypertension, hyperlipidemia, and a BMI indicating she is overweight. Along with diet and exercise, pharmalogical interventions can help reduce the risk of increased cardiovascular disease. In 2015, the EMPA-REG OUTCOME trial was published identifying intriguing data supporting the use of the SGLT2 inhibitor, empagliflozin, in significantly reducing rates of death from cardiovascular causes in type 2 diabetes mellitus patients (Zinman et al., 2015). A literature review was conducted on the current evidence SGLT2

inhibitor, empagliflozin, has on reducing cardiovascular outcomes and mortality in type 2 diabetes mellitus patients.

Findings

The EMPA-REG OUTCOME trial is currently the first and only published trial specifically assessing the cardiovascular safety profile in SGLT2 inhibitors. The trial was a non-inferiority, randomized, double-blind, placebo-controlled trial evaluating the cardiovascular effects once-daily empagliflozin (dosed at 10 mg or 25 mg) vs. placebo had on adults with type 2 diabetes at a high cardiovascular risk who were receiving standard care (Zinman et al., 2015). The primary outcome focused on death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke. 7020 study patients were observed in this trial, of whom were adults with type 2 diabetes mellitus, had a body-mass index less than 45, had a GFR of at least 30, had established cardiovascular disease, and had a Hemoglobin A1C between 7.0% and 10.0% (Zinman et al., 2015). It is important to note patients in this trial had established cardiovascular disease and cardiovascular risk factors, including hypertension and dyslipidemia, and were treated according to guidelines and standard care with the use of renin–angiotensin–aldosterone system inhibitors, statins, and aspirin (Zinman et al., 2015).

Early in the trial the results indicated those receiving empagliflozin with type 2 diabetes mellitus and at high risk for cardiovascular events, had a lower rate of mortality from cardiovascular related causes (Zinman et al., 2015). A 38% relative risk reduction in cardiovascular mortality and a 32% risk reduction in all-cause mortality among patients with type 2 diabetes mellitus and cardiovascular disease was observed in patients taking empagliflozin vs. placebo (Tucker, 2016; Simo & Hernandez, 2016; Martens, Mathieu, & Verbrugge, 2017; Secrest, Udell, & Filion, 2017). Although, there is limited data available to understand and

support exactly why empagliflozin demonstrated such a substantial cardiovascular benefit shortly after randomization, many experts have speculated on different hypotheses. McGovern et al. (2017) have commented that the cardiovascular benefits may have been achieved due to the diuretic effect SGLT2 inhibitors have, or rather suggesting SLGT2 inhibitors act on reducing cardiac preload and afterload, or simply more efficient use of ketone bodies relieves some of the strain on the myocardial tissue. Regardless, additional studies and research are needed to fully understand and support these hypotheses. Furthermore, the EMPA-REG OUTCOME trial did not show any significant differences in the rates of myocardial infarction or stroke (Zinman et al., 2015; Simo & Hernandez, 2016; Martens et al., 2017).

Zinman et al. (2015) suggests "the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional" (p. 2126) including, weight reduction by approximately 2-4 kg, reduction in systolic blood pressure by about 4-6 mm HG, an increase in plasma volume by about 0.8 g/dL of hemoglobin, and about a 1% reduction in hemoglobin A1C levels (Secrest et al., 2017; Martens et al., 2017).

Studies have also revealed significant reductions in heart failure admissions (decreased by about 33%) and end-stage kidney disease (Martens et al., 2017). With the use empagliflozin, results have suggested a reduction in vascular stiffness and improved endothelial function leading to an overall reduction in cardiac demand (Zinman et al., 2015). All of the abovementioned factors are known to improve cardiovascular risk.

The EMPA-REG OUTCOME trial has successfully provided data to support the use of empagliflozin long term, as well as compelling evidence that empagliflozin reduces cardiovascular risk and mortality (Zinman et al., 2015). Throughout the literature, it has been identified that empagliflozin is a reasonable choice for add-on therapy in patients with type 2

diabetes mellitus and a high cardiovascular risk (Naing et al., 2016; Simo & Hernandez, 2016; Secrest et al., 2017). Current guidelines and recommendations continue to recommend metformin as monothereapy until treatment has failed as the primary approach, at which point empagliflozin may be started as a second-line treatment (Secrest et al., 2017). Insufficient data is available to start any other antidiabetic agents first line or as monotherapy (Secret et al., 2017).

Adverse effects

It is noted throughout the literature that empagliflozin is generally well-tolerated. However, similar to any medication, it comes with a few notable adverse effects. Most notably, there is an increased rate of genital infections reported in those who were treated with empagliflozin vs placebo (Secrest et al., 2017). These infections were reported as mild to moderate in intensity and most commonly occurred in females (Scott, 2014; Kohler et al., 2016; Zimmermann, 2016). Over a time period of three years, 10% of women and 5% of men reported a genital mycotic infection (Zimmermann, 2016).

Secondly, a meta-analysis of more than 35,000 patients revealed a 15% relative risk for developing a urinary tract infection (Martens et al., 2017). Understandably, patients with a previous history of UTIs are more likely to develop these infections while on empagliflozin (Dixit et al., 2015). Complicated urinary tract infections, such as pyelonephritis or urosepsis, rates were similar in both placebo (1.8%) and empagliflozin (1.7%) (Naing et al., 2016).

Thirdly, volume depletion secondary to diuresis may also occur in patients at high risk, including the elderly, those using diuretics, or CKD patients (Martens et al., 2017). A meta-analysis conducted by Dixit et al. (2015) revealed approximately 0.5% of patients treated with 10 mg empagliflozin experienced adverse effects related to volume depletion, including dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope. Similarly, 0.3%

of patients treated with placebo and 25 mg empagliflozin experienced the same effects (Dixit et al., 2015). The incidence of volume depletion was similar between empagliflozin and placebo at baseline, however the incidence increased in patients who received a loop diuretic at baseline by 1.5% (Kohler et al., 2016). Therefore, assessment and correction of volume depletion prior to initiation of empagliflozin is recommended (Woo, 2015).

Lastly, since hypoglycemia is a concerning and potentially detrimental adverse effect, it is important to note that empagliflozin was not associated with an increased risk of hypoglycemia compared with placebo, unless used in combination with sulfonylurea and/or basal insulin, which are previously known to cause hypoglycemic episodes (Kohler et al., 2016).

Study Limitations/ Future Implications

The EMPA-REG OUTCOME trial was revolutionary in publishing data supporting empagliflozin and its effects on improving survival in adults with type 2 diabetes mellitus and cardiovascular disease. However, there are limitations and a need for future research to be completed.

The EMPA-REG OUTCOME trial only involved participants with high cardiovascular risk in their study. There is no clinical evidence or long-term data reporting morbidity and mortality in patients with low or no pre-existing cardiovascular disease. It is unknown if the use of SLGT2 inhibitors in this patient population would improve their cardiovascular risk profile (Secrest et al., 2017; Zimmermann, 2016; McGovern et al., 2017). It is plausible to expect similar benefits in the same high risk group, however, we cannot assume the same is true in a population with less risk (McGovern et al., 2017). A UK cross-sectional analysis of the EMPA-REG OUTCOME trial found that only a small proportion of the population had the same high cardiovascular risk as those involved in the EMPA-REG OUTCOME trial. Further data is needed

to identify possible cardiovascular benefits in those that do not fit this high cardiovascular risk profile (McGovern et al., 2017).

Furthermore, an article by Tucker (2016) reported that a little under half of the FDA panel members were skeptical about so quickly approving this new indication based on the research of a single study in a relatively new class of antidiabetic agents. Head-to-head trials of empagliflozin and other SGLT2 inhibitors have not yet been completed and published (Dixit et al., 2015). Upcoming trials, including the canagliflozin cardiovascular assessment study (CANVAS) and the Multicenter Trial to Evaluate the Effect of Dapagliflozin (DECLARE-TIMI58), will provide evidence of these outcomes and hopefully elude to whether these benefits are related to empagliflozin alone or are a class effect (Martens et al., 2017).

Future research is also warranted to identify the use of empagliflozin in specific patient populations (e.g. children, adolescents, elderly), those with multiple co-morbidities, those with CKD (the data published is limited), the use of empagliflozin in combination with other antidiabetic agents, aside from metformin, as well as understanding the cardiovascular benefits when used as monotherapy (Dixit et al., 2015; Simo & Hernandez, 2016; McGovern et al., 2017; Secrest et al., 2017).

Discussion

The presented evidence and review of the literature demonstrates empagliflozin is an excellent antidiabetic add-on agent in patients who have type 2 diabetes mellitus and have a high cardiovascular risk profile. Numerous systematic reviews and meta-analyses support the cardiovascular safety of empagliflozin (Secrest et al., 2017). Although, more research and trials broadening the population group are needed to determine if the use of empagliflozin and its

associated cardiovascular benefits are similar, the use of empagliflozin to reduce cardiovascular mortality in high risk populations is clear.

Learning Points

- Continue to recommend metformin as monothereapy until treatment has failed as the primary approach, at which point empagliflozin may be started as a second-line treatment
- The literature and evidence supports the use of empagliflozin as add-on agent to metformin in patients with **high** cardiovascular risk to reduce the rate of mortality and morbidity
- Empagliflozin significantly reduced rates of death from cardiovascular disease, reduced hospitalizations for heart failure, and reduced death related to any cause
- For patients with low cardiovascular risk, no clinical evidence currently supports the preferential use of SGLT2 inhibitors to improve cardiovascular risk profiles

References

Dixit, D., Yoon, Y., Volino, L.R., & Mansukhani, R.P. (2015). Empagliflozin: a sodium-glucose cotransporter 2 inhibitor for treatment of type 2 diabetes. *American Journal of Health-System Pharmacy, 72*(22), 1943-1954.

Khardori, R. (2017). Type 2 diabetes mellitus. *Medscape.* Retrieved from http://emedicine.medscape.com/article/117853-overview#a6

Kohler, S., Salsali, A., Hantel, S., Kaspers, S., Woerle, H.J., Kim, G., & Broedl, U.C. (2016). Safety and tolerability of empagliflozin in patients with type 2 diabetes. *Clinical Therapeutics, 38*(6), 1299-1313.

Martens, P., Mathieu, C., & Verbrugge, F.H. (2017). Promise of SLGT2 inhibitors in heart failure: diabetes and beyond. *Current Treatment Options in Cardiovascular Medicine, 19*(3), 23. doi: 10.1007/s11936-017-0522-x.

McGovern, A., Feher, M., Munro, N.,& Lusignan, S. (2017). Sodium-glucose co-transporter 2 (SGLT2) inhibitor: comparing trial data and real-world use. *Diabetes Therapy, 8*(2), 365-376.

Naing, S., Poliyedath, A., Khandelwal, S., & Sigala, T. (2016). Impact of EMPA-REG OUTCOME ® on the management of type 2 diabetes mellitus: a review for primary care physicians. *Postgraduate Medicine, 128*(8), 822-827.

Scott, L.J. (2014). Empagliflozin: A review of its use in patient with type 2 diabetes mellitus. *Drugs, 74*(15), 1769-1784.

Secrest, M.H., Udell, J.A., & Filion, K.B. (2017). The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agnoists, and SGLT2 inhibitors. *Trends in Cardiovascular Medicine, 27*(3), 194-202. doi: 10.1016/j.tcm.2017.01.009

Simo, R., & Hernandez, C. (2016). New treatment for type 2 diabetes mellitus and cardiovascular disease. The revolution has begun. *Revista Espanola de Cardiologia, 69*(11), 1005-1007.

Tucker, M.E. (2016). FDA approves empagliflozin for reducing CVD death. *Medscape.* Retrieved from http://www.medscape.com/viewarticle/872697

Woo, V. (2015). Empagliflozin/linagliption single-tablet combination: first-in-class treatment option. *The International Journal of Clinical Practice, 69*(12), 1427-1437.

Zimmermann, J. (2016). Empagliflozin (Jardiance) for type 2 diabetes mellitus. *American Family Physician, 94*(12), 1014-1015.

Zinman, B., Wanner, C., Lachin, J.M., Fitchett, D., Bluhmki, E., Hantel, S.,…Inzucchi, S.E. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *The New England Journal of Medicine, 373,* 2117-2128. doi: 10.1056/NEJMoa1504720