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The use of SGLT2 Inhibitors compared to GLP-1 receptor agonists in patients with type 2 diabetes and hypertension

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The use of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors Compared to Glucagon-like Peptide 1 (GLP-1) Receptor Agonists in Patients with Type 2 Diabetes and Hypertension

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Abstract

Hypertension and Type 2 diabetes mellitus (T2DM) coexist frequently and both increase the incidence of cardiovascular disease. Recently developed drugs in the GLP-1 receptor agonists class and SGLT2 inhibitor class have been noted to have hypotensive actions (Katayama et al., 2018). Controlling blood pressure and glucose are increasingly important for the treatment of diabetes accompanied by hypertension. A case report was analyzed and the topic of sodium–glucose cotransporter 2 (SGLT2) inhibitors compared to glucagon-like peptide-1 (GLP-1) receptor agonists for the selection of a second line treatment for T2DM patients with hypertension was formulated. A literature review was done using databases such as CINAHL and PubMed. The literature in these articles and guidelines outlined below demonstrates the wide variety of benefits of both SGLT2 inhibitors and GLP-1 agonists within the T2DM population. While both pharmacological classes have benefits, they also have contradictions. SGLT2 inhibitors and GLP-1 receptor agonists independently improve cardiovascular outcomes and do so by separate mechanisms. Guidelines recommend due to the unique side effects and benefits of each medication class the health care provider decision requires an individualized approach to select the appropriate medication class.

Background

Type 2 diabetes mellitus (T2DM) and hypertension coincide frequently. According to Bailey & Marx (2019) “among individuals with T2DM nearly 40% have hypertension at the time of DM diagnosis” (p.1). Even if blood pressure was initially normal, it often rises with the advancement of diabetic nephropathy, resulting in hypertension (Katayama et al., 2018). Cardiovascular related adverse effects are approximately double within the T2DM population. The cardiovascular events are related to microvascular and macrovascular damage which result

in myocardial infarction, stroke, and heart failure (Bailey & Marx 2019). Almost half of T2DM patients will die from a MI (Scheen, 2018). Reducing the risk for major adverse cardiac events is now directed from a comprehensive approach beyond glucose control. Since 2008 and 2012 the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) have mandated that any new medication used for the treatment of T2D must have a cardiovascular outcome trial to demonstrate its safety and MACE (Sinha & Ghosal, 2019).

Comparing hypertension in diabetic patients to normotensive non-diabetics, “the rate of onset of cardiovascular disease is 5–7 times higher in diabetic patients with hypertension” (Katayama et al., 2018, p.216). Hyperglycemia elevates blood pressure within diabetes due to arterial stiffness, sodium retention, leading to a volume expansion and a greater volume of exchangeable sodium (Briasoulis et al., 2018). Clinical trials have demonstrated that with decreasing blood pressure, there is an improvement of hyperglycemia and reduction of the micro- and macrovascular complications of diabetes. Early treatment of hypertension and diabetes will prevent and delay the progression of cardiovascular disease and potential diabetic nephropathy (Katayama et al., 2018).

Recent pharmacological advancement in treatment of T2DM has demonstrated many cardiovascular benefits including the success of intensive blood pressure control for reducing the micro- and macrovascular complications of diabetes (Briasoulis et al., 2018). The two pharmacological categories that have seen these results are the SGLT2 inhibitors and the GLP-1 receptor agonists. SGLT2 inhibitor studies have shown results in sustained systolic and diastolic blood pressure reduction and meta-analysis data does note GLP-1 receptor agonists have a beneficial effect on systolic blood pressure in patients with T2DM (Gurgle et al., 2016). Both SGLT2 inhibitors and GLP-1 receptor agonists can improve glycemic control and reduce blood

pressure, body weight, and major adverse cardiac outcomes. However, it is not obvious which of the two classes should be preferred in a T2DM patient with established cardiovascular disease (Scheen, 2018).

This literature review will incorporate a case report describing a woman in her late fifties who has a history of hypertension and T2DM. She subsequently presented to her primary provider for a fever. It was not known at the time if she had been adherent to her current medications. During the visit she was diagnosed with cellulitis and probable sepsis. Treatment was initiated in the emergency room. The purpose of this review is to compare the clinical trials and real-world effectiveness of SGLT2 inhibitors compared to GLP-1 agonists, related to their effectiveness within the T2DM-HTN population.

Case Report

J.B. was a 58-year-old obese female who presented to the clinic accompanied by her sister for fever, chills, and confusion for one day. The patient had a past medical history of Type 2 diabetes, hypertension, and hyperlipidemia. Patient reports a fever that has been present for one day for which she has been using Ibuprofen (last dose within 2-3 hours). She states that despite using ibuprofen the fever remains elevated with a measured fever of 104.7 F upon clinic visit. She states her family had concerns of her being confused within the past day. She describes the confusion as ‘forgetfulness’ and does not feel it is a concern. She does report forgetfulness, mild fatigue, and feeling chilled requiring blankets. There are no known ill contacts at home.

She denies cough, wheezing, shortness of breath, chest pain, palpitations, abdominal pain, nausea, vomiting, diarrhea, polyuria, dysuria. She denies headache, change in vision, neck pain, dizziness or lightheadedness. She reports no swelling, numbness/tingling in her extremities, sores on her feet. She denies concerns of confusion and or forgetfulness.

J.B. is currently on medication including the following: ezetimibe 5 mg tablet, metoprolol 50 mg two times daily, Lisinopril 10 mg daily, Metformin 1000 mg daily, Fish oil 1000 mg daily, Zocor 80 mg daily, Aspirin 325mg daily. She reports no known allergies, no current tobacco use, states she quit smoking in 2002. She is currently up to date on immunizations including influenza and pneumonia. She denies recent hospitalizations or antibiotic use. She has a surgical history of tubal ligation > 10 years. Her family history does include type 2 diabetes and cardiovascular disease in her father.

A complete physical examination was performed after obtaining the patient's history. J.B.'s vital signs included: height 5'5", weight 118 kg (260 lbs), a BMI of 43.4 kg/m, blood pressure 194/83, pulse 119, respirations 14, temperature 104.7 F, O2 93% on room air. Obese female with well-kept appearance is resting quietly in clinic room. She does not appear to be in distress. Her skin is pale, hot, and diaphoretic. She is awake, alert and oriented to self, place, and time. She answers questions appropriately. Head is atraumatic and the neck is supple without masses. The thyroid was nonpalpable and no lymphadenopathy is palpated. There is no JVD observed or carotid bruit found. Red reflex present bilaterally, with her pupils equal, round and reactive to light and fundi were clear and with no arteriovenous nicking or retinopathy. Her EOM's are intact. The ears are symmetrical, no tenderness or discharge, normal tympanic membranes with positive light reflex. Patent nares with moist and pink mucosa. Her lungs were clear to auscultation, no wheezes, crackles or rhonchi noted, with even and unlabored respirations. S1 and S2 were heard, heart rate and rhythm were regular with no extra heart sounds, murmurs, or gallops. Abdomen was globulous, soft, nondistended, nontender. Bowel sounds were present in all four quadrants. No CVA tenderness was noted on percussion. The lower left extremity has edema with significant erythema and tenderness to the soft tissues

measuring an area of 8 cm x 6 cm. Distal pulses are 2+. Musculoskeletal system reveals no obvious deformity with strength equal bilaterally. Gait was observed to be steady on arrival. Cranial nerves I-XII are grossly intact.

Differential diagnosis

Cellulitis, MRSA rule out, sepsis, Chills with fever, Uncontrolled Type 2 diabetes mellitus, Uncontrolled Essential hypertension.

Labs/Imaging

Labs were obtained during the office visit CBC, CRP, CMP, lactic acid, and ESR and were as follows: WBC 12.5 K/uL*, CRP 144.4 mg/dL*, glucose 266 mg/dL*, sodium 132 meq/L*, chloride 94 meq/L*, CO2 20 meq/L*, anion gap 22 meq/L*, lactic aicd 4.4 mmol/L*, ESR 57 mm/Hr*. There was no imaging obtained at that time.

Plan

Based on J.B.'s medical history, physical exam of new skin infection, high temperature despite recent antipyretics, increased heart rate, and decreased oxygen saturation this patient was sent to the emergency department for further evaluation of potential sepsis. Based on J.B.'s medical history, physical exam of new skin infection, high temperature despite recent antipyretics, increased heart rate, and decreased oxygen saturation this patient was sent from the clinic to the emergency department for further evaluation of potential sepsis. Hospitalization was required for IV fluids, antibiotics, wound cultures with sensitivity, monitoring of blood glucose and renal function.

Following hospitalization, JB will be seen in 1-2 weeks after hospital discharge and then a minimum of every 3 months until stabilized. We will coordinate care with the diabetes educator, dietician, and wound care specialists. Receiving the proper education from these

specialties will provide her with the tools to improve her health and reduce complications. HgB A1C and BMP should be drawn every 3 months to monitor glucose control and renal function. Regulation of glucose and hypertension is prudent to reducing cardiovascular risk. She may require addition of an SGL2 inhibitor and/or GLP-1 receptor agonist to current medication regime in order to obtain tighter glucose control. Weight loss and proper nutrition can also help to better control of both hypertension and hyperglycemia.

Literature Review

Topic Formulation

According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) an update to the 2018 recommendations was requested due to the research findings in 2019 of cardiovascular outcome trials (Buse et al., 2020). There is a fundamental change in T2DM management, moving from a goal of glucose control to an objective of cardiovascular and renal protection (Bailey & Marx 2019). Newer diabetes mellitus agents such as SGLT2 inhibitors and GLP-1 receptor agonists have been demonstrated to have cardio-protective effects. The impact of tight blood pressure control with persons of T2DM and hypertension remains to be interpreted (Buse et al., 2020). Again, this literature review is focused on exploring the evidenced behind the selection of a second line treatment for T2DM patients with hypertension.

Literature Search

A literature review was performed to gather evidence and articles relevant to the use of a SGLT2 inhibitor compared to a GLP-1 receptor agonist in diabetic patients with hypertension and cardiovascular risk. Literary sources were gathered using the PubMed and CINAHL

(Cumulative Index to Nursing & Allied Health), provided from the UND School of Medicine and Health Sciences online resources.

A variety of keywords were used to search for sources including the following: “SGLT2 inhibitors”, “GLP-1 receptor agonists”; “hypertension”, “cardiac outcomes”, “trial outcomes.” Articles used for the analysis of the literature were no more than five years old and were limited to English text only. The intention of these limitations was to provide evaluation that utilized current and relevant information. A total of 258 articles resulted from a search within PubMed using “SGLT2 inhibitors” and “GLP-1 receptor agonists.” To narrow this large number of results, a search then included the key words “cardiac outcome” and which resulted in a selection of 41 articles. A total of 7 articles were reviewed within the search criteria limitations that were put in place and were used throughout the literature review process. An additional search in PubMed was performed using “SGLT2 inhibitors”, “GLP-1 receptor agonists”; “hypertension”, and a total of 2 articles were reviewed and selected for further literature evaluation. The database of CINAHL was then reviewed for further articles related to “SGLT2 inhibitors”, “GLP-1 receptor agonists”; “trial outcomes”, a total of 7 articles were resulted and 2 articles were selected and were utilized in the literature review. A total of 11 articles were finally selected for the literature review of this paper.

Synthesis of Current Literature

SGLT2 inhibitors are one of the first anti-hyperglycemics to demonstrate significant cardiovascular benefits in multiple cardiovascular outcomes trials. The primary mechanism of action within SGLT2 inhibitors is the inhibition of sodium-glucose cotransporter 2 in the kidneys to prevent reabsorption of glucose and facilitate its excretion in urine (Nagahisa & Saisho, 2019). The beneficial cardiovascular outcomes were subsequently identified within multiple different

trials. The mechanisms of action for cardiovascular benefits are osmotic diuresis leading to improved hemodynamic function, reduction of blood pressure, beneficial weight loss, and a shift in body fuel with ketosis (Dhindsa et al., 2019). SGLT2 inhibitors decrease blood pressure through osmotic diuresis. Other factors to be noted is a reduction in arterial stiffness and improvement in endothelial dysfunction which was been demonstrated in recent studies (Lim et al., 2018).

GLP-1 is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. GLP-1 receptor agonists initially were developed as glucose-lowering medications. They since have been associated with multidimensional actions (Sinha & Ghosal, 2019). Through animal studies and small clinical studies, GLP1-receptor agonists have been found to reduce inflammation in the vascular endothelium. This results in the improvement of endothelial function, plaque stability, blood flow and platelet aggregation They have positively lowered glucose, body weight, and recent studies have shown positive implications of reducing blood pressure (Garg et al., 2019)

The three largest CVD outcome trials of SGLT2 inhibitors are Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, and the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI) 58 trial (Garg et al., 2019). In EMPA-REG OUTCOME the study resulted with a 38% reduction in cardiovascular mortality, 32% reduction in all-cause mortality, and a 35% reduction in heart failure hospitalizations were observed in those blood randomized to empagliflozin (Dhindsa et al., 2019). The use of empagliflozin decreased blood pressure 2-3 mmHg in the treatment group (Lim et al., 2018). The CANVAS similarly mimicked the EMPA-REG OUTCOME results and showed a 33% reduction in heart

failure hospitalizations in those patients randomized to canagliflozin (Dhindsa et al., 2019). Canagliflozin therapy decreased systolic blood pressure by 3.93 mmHg and diastolic blood pressure by 1.39 mmHg (Lim et al., 2018).

DECLARE-TIMI 58 trials had available data on left ventricular ejection fraction which marked the importance of this medication class in heart failure. Dapagliflozin reduced hospitalizations for heart failure in patients with and without reduced ejection fractions and reduced cardiovascular disease death (Dhindsa et al., 2019). Dapagliflozin and ipragliflozin treatment were noted to have a 2-5 mmHg reduction in blood pressure (Lim et al., 2018).

Several trials have been performed using GLP-1 agonists in patients with T2DM with either established or elevated risk factors for cardiovascular disease. These trials include: Liraglutide Effect and Action in Diabetes, Evaluation of Cardiovascular Outcomes Results-A Long-Term Evaluation (LEADER), Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), and HARMONY (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease) (Dhindsa et al., 2019). The LEADER trial's three-point major adverse cardiac events were reduced by 13% in the liraglutide group, with a 22% reduction in cardiovascular death and a 15% reduction in total mortality (Bailey & Marx 2019). The LEADER trial hallmarked liraglutides significant reduction in all-cause mortality predominantly driven by a reduction in cardiovascular deaths (Nagahisa & Saisho, 2019).

The SUSTAIN-6 trial semaglutide group compared to the placebo demonstrated a significant reduction in major adverse cardiac events by 26% after 2.1 years with a 39% reduction of non-fatal stroked (Bailey & Marx 2019). The trial also demonstrated a 36% reduction in the risk of new or worsening nephropathy which subsequently helps decrease blood pressure (Nagahisa & Saisho, 2019). The trial noted a mean reduction of 2.6 mmHg in systolic

blood pressure (Garg et al., 2019). The HARMONY trial demonstrated major adverse cardiac events were reduced by 22% and significant reduction in myocardial infarction (Dhindsa et al., 2019).

A thorough review of the literature revealed that previous trials of diabetic medications such as the SGLT2 inhibitors and GLP-1 receptor agonists goal was glucose control. Most trials were not driven to assess blood pressure outcomes (Gurgle et al., 2016). Over the past decade the treatment for patients with T2DM with established or at a high risk for cardiovascular disease has entirely changed to cardiovascular prevention and reduction, and ultimately decreasing major adverse cardiac events (Garg et al., 2019). The current studies of SGLT2 inhibitors and GLP1 receptor agonists have proven their efficacy to reduce major adverse cardiac events. Blood pressure control is a crucial factor for cardiovascular complications which makes hypertension one of most important risk factor for arteriosclerosis in diabetics (Scheen, 2018).

Recently developed GLP-1 receptor agonists and SGLT2 inhibitors have hypotensive actions, making them ideal for use in diabetics with hypertension (Katayama et al., 2018). The literature review confirms that treatment with SGLT2 inhibitors results in sustained systolic and diastolic blood pressure reduction (Briasoulis et al., 2018). The presumed factors for the decreased blood pressure are part osmotic diuresis and glucose excretion; followed by natriuresis and reduced intravascular volume, ameliorated arterial elasticity, and reduced cardiac preload and afterload (Nagahisa & Saisho, 2019). Literature also confirmed SGLT2 inhibitors offer a renal protective effect with significant reductions in the onset and or progression of nephropathy with empagliflozin and canagliflozin (Bailey & Marx 2019). Lastly, it was confirmed the use of SGLT2 inhibitors in patients with T2DM resulted in a reduction of 3 to 6 mmHg reduction in

systolic blood pressure and a 0 to 2 mmHg drop in diastolic blood pressure (Briasoulis et al., 2018).

With all medications there are side effects and risks and benefits to be weighed. The review from Dhindsa et al., (2019) discussed that the SGLT2 inhibitors have reported a 5% occurrence of candida vaginitis in women and a 10% of balanitis in men. Canagliflozin in the CANVAS Program was associated with an increased risk of lower limb amputation compared to the placebo. It is important to emphasize overall amputation risk was correlated with a prior history of amputation at baseline (Nagahisa & Saisho, 2019). The literature review from Buse et al., (2020) discussed that in the CREDENCE trial with canagliflozin although the risk of amputation was higher overall than in other SGLT2 inhibitors no significant increase in risk was observed with canagliflozin compared to the placebo.

Results of a meta-analysis of clinical trials and studies showed GLP-1 receptor agonists positively reduce blood pressure and body weight, have an anti-atherothrombotic effect, and have few episodes of hypoglycemia (Dhindsa et al., 2019). Garg et al., (2019) confirmed that GLP-1 receptor agonists additionally decrease atherosclerosis, myocardial ischemia, inflammation, endothelial dysfunction, and blood pressure. In reviewing the cardiovascular outcomes trials systolic blood pressure was noted to be between 0.8 and 2.6 mmHg less than the placebo group. The largest blood pressure difference was seen in the use of semaglutide in the SUSTAIN-6 trial, with an average reduction of 2.6 mmHg in systolic blood pressure, which may occur through increased renal excretion of sodium and endothelial vasodilation (Garg et al., 2019). An additional meta-analysis by Sinha & Ghosal (2019) highlighted that the class of GLP-1 receptor agonists reduce risk of atherosclerotic cardiovascular disease by cause a significant reduction in myocardial infarction and stroke.

Through the literature review, in the SUSTAIN-6 trial with the GLP-1 receptor agonist semaglutide, the common side effects were nausea, vomiting, and diarrhea (Dhindsa et al., 2019). The LEADER trial noted with the use of liraglutide, there was a significant increase in acute gallstones and acute cholecystitis. The SUSTAIN-6 trial also showed that semaglutide was associated with increased retinopathy complications but was largely in those individuals with retinopathy at baseline (Nagahisa & Saisho, 2019). An additional animal trial discussed that GLP-1 receptor agonists have been associated with medullary thyroid cancer and for now, should be avoided or used in caution with any history of medullary thyroid cancer or multiple endocrine neoplasia (Dhindsa et al., 2019).

In providing recommendations to patients regarding drug therapy, providers should engage in shared decision making and must balance drug efficacy with potential side effects. SGLT2 inhibitors and GLP-1 receptor agonists are the first anti-hyperglycemic to demonstrate significant cardiovascular benefit and hypotensive properties. Both medication classes are indicated for T2DM-HTN patients. Given the side effects and benefits from both agents the appropriate selection for reduction of blood pressure and cardiovascular risk reduction requires an individualized approach.

Learning Points

- SGLT2 inhibitors and GLP-1 receptor agonists are the first anti-hyperglycemic to demonstrate significant cardiovascular benefit and hypotensive properties.
- Given the side effects and benefits from both agents the appropriate selection for reduction of blood pressure and CV risk reduction requires an individualized approach.

- The cardiovascular benefits seen with both SGLT2 inhibitors and GLP-1 agonists make the prospect of combination therapy with these agents particularly appealing in patients with T2DM.
- Given the results from recent studies the American Diabetes Association and the European Association for the Study of Diabetes, recommend that patients with T2DM and clinical cardiovascular disease with inadequate glucose control despite treatment with metformin, should receive an SGLT2 inhibitor or GLP-1 receptor agonist.

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