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Sodium-Glucose Cotransporter 2 Inhibitors as Preferred Add-on Therapy to Metformin in Patients with Type 2 Diabetes Mellitus Who do not Reach Glycemic Goals with Metformin Alone

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Nursing 997: Independent Study

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PERMISSION

Title Sodium-Glucose Cotransporter 2 Inhibitors as Preferred Add-on Therapy to Metformin in Patients with Type 2 Diabetes Mellitus Who do not Reach Glycemic Goals with Metformin Alone

Department Nursing

Degree Master of Science

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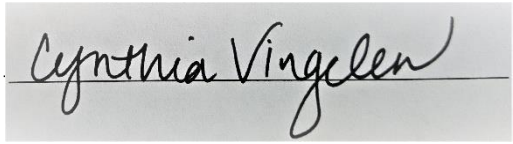
Signature 

Date 04/04/2017

Sodium-Glucose Cotransporter 2 Inhibitors as Preferred Add-on Therapy to Metformin in Patients with Type 2 Diabetes Mellitus Who do not Reach Glycemic Goals with Metformin Alone

Abstract

Diabetes is a national and global health care crisis. Scientists, researchers, and clinicians continue to seek the best therapies to optimize diabetes treatment to obtain glycemic goals with the least potential for adverse effects, resulting in decreased target end-organ damage, morbidity, and mortality. Sodium-glucose cotransporter-2 (SGLT2) inhibitors comprise a novel drug class and have shown promise in treating type 2 diabetes. They work by increasing glucose excretion through reduced glucose reabsorption in the kidney (Imprialos, Sarafidis, & Karagiannis, 2015), independent of pancreatic beta-cell function and insulin resistance, making them effective for use at all stages on the diabetes continuum, even in late-stage disease. Numerous studies have shown that SGLT2 inhibitors also provide a meaningful reduction in blood pressure; an advantageous effect for patients with comorbid hypertension (Heerspink, Perkins, Fitchett, Husain, & Cherney, 2016). Beta-cell function is estimated to be reduced by 50-60% at the time of diagnosis and continues to decline thereafter (Popa & Mota, 2013). An SGLT2 inhibitor, which works independently of beta-cell function, is an excellent treatment option if patients fail to achieve adequate control with diet, lifestyle, and Metformin therapy.

Background

Diabetes directly affects approximately 12.6% of adults over the age of 20 in the United States; is the primary diagnosis associated with over 37 million visits to provider offices, hospital outpatient, and emergency departments yearly; and remains the seventh leading cause of death in the United States (Centers for Disease Control and Prevention [CDC], National Center for Health Statistics, 2017). More than 29 million Americans and 422 million people worldwide are estimated to have diabetes (WHO, 2016). Type 2 diabetes accounts for 90-95% of these cases (CDC, 2014b).

Type 2 diabetes mellitus is a chronic, complex metabolic disorder characterized by insulin secretion deficiencies, insulin resistance, or a combination of both, leading to impaired glucose homeostasis and hyperglycemia (ADA, 2014). The potential complications of inadequately controlled diabetes have been well-documented and include increased risk of macrovascular complications, such as coronary artery disease and stroke. Uncontrolled diabetes can also lead to increased risk of microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy. Improved glycemic control has been extensively shown to prevent the risk or reduce the progression of diabetes-associated microvascular complications (Dunphy, Brown, Porter, & Thomas, 2015). Cardiovascular complications, retinopathy, and nephropathy associated with diabetes can be further reduced with control of associated hypertension and dyslipidemia.

Despite the advances made in diabetes research and treatment, the prevalence of the disease and, subsequently, its associated morbidity continue to rise (Guariguata, Whiting, Hambleton, Beagley, Linnenkamp, & Shaw, 2014). With this rise, researchers and clinicians are tasked with finding new, effective, and safe treatment options to minimize the disease burden.

First-line therapy continues to include diet modification, focused on controlling carbohydrate intake, and exercise coupled with Metformin drug therapy (American Association of Clinical Endocrinologists, 2017; ADA, 2015). Even with the addition of oral antidiabetic agents, including glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 analogs used in combination therapy with Metformin, half of patients in the United States do not reach goal A1C levels (<7%), and one out of four eventually requires insulin therapy (CDC, 2014a).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors comprise a new class of medications for the treatment of type 2 diabetes. These inhibitors show promise as staples in diabetes management. SGLT2 inhibitors increase glucose excretion by the kidneys, work independently of pancreatic beta-cells, and are not affected by insulin resistance, making them an attractive choice at all stages on the diabetes continuum. As SGLT2 inhibitor use proliferates in diabetes therapy, the number of studies evaluating their safety, efficacy, and place in type 2 diabetes management continues to increase. This report seeks to review this available evidence to determine if SGLT2 inhibitors should be recommended as preferential second-line add-on therapy for the management of type 2 diabetes in patients when Metformin therapy alone is insufficient to meet treatment goals.

Literature Review

Relevance to Case

The appendix included as an adjunct to this paper details the case of Dorothea, a patient with type 2 diabetes mellitus who is not meeting glycemic goals with her current regimen.

Dorothea was diagnosed with type 2 diabetes approximately 10 years ago and has concomitant hypertension. Dorothea has been managing her type 2 diabetes with diet and exercise as well as Metformin monotherapy dosed at 500 mg twice daily since her diagnosis 10 years ago. Unfortunately, when she was recently seen in clinic, her hemoglobin A1C was 8.5%, an increase from 8.2 at her last check, and home glucose levels were ranging between 150 and 200 mg/dL. In addition to inadequate control of her diabetes, Dorothea's blood pressure was elevated in clinic with a repeat check confirming the elevation. Hypertension treatment was Lisinopril 20 mg once daily. An appropriate step-up in Dorothea's treatment at this time includes increasing her Metformin dose (if tolerated without unacceptable GI side effects) and adding hydrochlorothiazide for improved control of diabetes and hypertension, respectively. However, a consideration for the addition of an SGLT2 inhibitor would be reasonable if adequate control is not achieved with the current treatment modifications. Addition of an SGLT2 inhibitor in Dorothea's case could potentially improve control of both diabetes and hypertension. Its conceivable use as a preferred second-line add-on therapy to ongoing Metformin use will be discussed in this review.

Literature Search

A literature search was conducted via the University of North Dakota's Harley E. French Library website. Databases employed in the search included the Cochrane Library database, the Cumulative Index to Nursing & Allied Health Sciences (CINAHL), and PubMed. Search terms and mesh terms used were type 2 diabetes mellitus, Metformin, sodium-glucose cotransporter 2 inhibitors, and add-on therapy. A variety of combinations of the above terms was utilized. Results were narrowed to include articles published in 2014 or later and were further narrowed to exclude articles focusing on specific SGLT2 inhibitors without generalization to class.

Preference was given to meta-analyses and reviews. Selected articles were searched for cross-references.

Synthesis of Current Literature

Efficacy.

Hemoglobin A1C and blood glucose. Reduction of Hemoglobin A1C (HbA_{1C}) (most often to less than 7%, but individualized based on comorbidities) is typically identified as the primary goal of diabetes management due to its extensive effects on decreasing microvascular complications and, to a lesser extent, macrovascular complications (Wildin, Panicker Rajeev, & DeFronzo, 2016). Myriad studies have shown that SGLT2 inhibitor use as an add-on to Metformin is superior to placebo plus Metformin and at least as effective as glimepiride plus Metformin (Brietzke, 2015) and sitagliptin plus Metformin (Sevald, Jackson, & McAna, 2016) in regards to lowering HbA_{1C} and fasting glucose levels (Lisenby, Meyer, & Slater, 2016; Whalen & St. Onge, 2015; Zhang, Dou, & Lu, 2014). In Zhang et al.'s (2014) meta-analysis on available randomized controlled trials, HbA_{1C} lowering effects persisted after one year to a statistically significant extent and fasting glucose reductions persisted after two years. Moreover, analyses of more recent studies indicated superiority of SGLT2 inhibitor-Metformin combination to DPP-4 inhibitor–Metformin and sulfonylurea–Metformin combinations in decreasing fasting blood glucose and HbA_{1C} (Wilding et al., 2016; Qaseem, Barry, Humphrey, & Fociea, 2017). Wilding et al. (2016) further supported the role of SGLT2 inhibitors for glucose reduction, elucidating that reductions in glucose are greatest at higher baseline levels because glucose excretion is eliminated as a percentage of the total glucose load, signifying that SGLT2 inhibitors are effective in those with poorly controlled diabetes.

Body weight. Lifestyle changes, including diet, weight loss, and exercise have been the mainstay of diabetes management for years and continue to be considered first-line therapy in diabetes treatment, with the addition of Metformin when these are unsuccessful at reaching glycemic goals. Obesity increases the risk of developing diabetes, hypertension, hyperlipidemia, heart disease, and stroke. Therefore, choosing medications that are weight-neutral or weight-favorable is ideal. SGLT2 inhibitors have been shown across studies to favorably impact weight, presumably via caloric loss through glucosuria (Hasan, Alsahli, & Gerich, 2014). Meta-analyses evaluating numerous randomized controlled trials (RCTs) have consistently shown superiority in regards to weight loss of SGLT2 inhibitor-Metformin combination versus glipizide-Metformin, sulfonylurea-Metformin, and placebo-Metformin combinations (Brietzke, 2015; Maruther et al., 2016; Qaseem et al., 2017; Wilding et al., 2016; Zhang et al., 2014).

Blood pressure, heart rate, and cardiovascular effects. Type 2 diabetes mellitus is a well-known risk factor for cardiovascular disease. Adequate control of diabetes and associated cardiovascular risk factors, such as hypertension and dyslipidemia, are paramount to decreasing the incidence of major adverse cardiac events. A plethora of studies have assessed the effects of antidiabetic medications on blood pressure, and more recently, on cardiovascular outcomes, such as heart attack and stroke. Across all class members, SGLT2 inhibitors have been shown to decrease blood pressure irrespective of underlying hypertension, have done so to a greater extent in those with higher baseline pressures, and have had little rebound effect on heart rate (Imprialos, 2015; Tikkanen, Chilton, & Johansen, 2016). Numerous additional reviews and meta-analyses continue to support these findings (Lisenby et al., 2016; Sevald et al., 2016). Head-to-head comparisons of Metformin-SLGT2 inhibitor combinations versus Metformin-sulfonylurea and Metformin-DPP4 inhibitor combinations have indicated preference for Metformin-SGLT2

inhibitor combinations in respect to blood pressure and heart rate outcomes and have shown that SGLT2 inhibitors as an add-to Metformin were clearly superior to Metformin alone (Maruther et al., 2016; Qaseem et al., 2017).

Results of a recently completed landmark trial evaluating the impact of the SGLT2 inhibitor Empagliflozin on cardiovascular outcomes could have a major impact on treatment guidelines for patients with diabetes and comorbid heart disease or cardiovascular risk factors. As described by Scheen (2016), the EMPA-REG OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes), comprised of over 7000 patients with cardiovascular disease and type 2 diabetes, sought to identify the effects of empagliflozin versus placebo on the primary composite outcome triple MACE (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). Researchers reported a 14% reduction in triple MACE, as well as more than 30% reductions in cardiovascular mortality, overall mortality, and hospitalizations related to heart failure in the cohort treated with empagliflozin (Heerspink et al., 2016; Scheen, 2016). According to Scheen (2016), these protective effects were observed regardless of the patient's blood pressure at baseline. Additionally, patients in the empagliflozin treatment group used anti-hypertensives less frequently than those in the placebo group, which could have blunted the overall reported effect of blood pressure lowering of empagliflozin (Scheen, 2016). Of interest, stroke risk was not noted to be decreased in the treatment group of the EMPA-REG trial; an outcome some theorize could be due to the study population's relatively well-controlled blood pressures at baseline (Scheen, 2016).

The other SGLT2 inhibitors approved for use by the FDA in the United States are currently undergoing their own detailed trials to evaluate effects on cardiovascular outcomes. The Canagliflozin Cardiovascular Assessment Study, due to be completed in June of 2017, is

looking at the effect of canagliflozin on CV death, nonfatal myocardial infarction, and nonfatal stroke in patients at risk for or with underlying cardiovascular disease and comorbid uncontrolled diabetes (Lisenb et al., 2016). The DECLARE-TIMI 58 trial is evaluating the effect of dapagliflozin on cardiovascular death, myocardial infarction, and ischemic stroke in those with type 2 diabetes and two or more cardiovascular risk factors or known cardiovascular disease (Lisenb et al., 2016). It is set to be completed in April of 2019.

Renoprotection. Not only has the class of SGLT2 inhibitors been shown to have renoprotective effects, these drugs have been proven safe in many placebo-controlled studies for use in patients with an estimated glomerular filtration rate (eGFR) as low as 30 $mL \cdot min^{-1} \cdot 1.73m^{-2}$ (Heerspink et al., 2016). They are, however, likely to be ineffective at eGFR levels less than 30 $mL \cdot min^{-1} \cdot 1.73m^{-2}$ due to their mechanism of action and reliability on renal filtration rates to excrete urinary glucose (Whalen & St. Onge, 2015). In reviews by Wildin et al. (2016) and Heerspink et al. (2016), authors explicated that SGLT2 inhibitors have been shown to decrease glomerular hyperfiltration, end-stage renal disease, renal death, and acute kidney injury. Heerspink et al. further discussed the effect of SGLT2 inhibitor use in the reduction of uric acid levels, an acid that has been associated with hypertension, renal disease, and cardiovascular disease (2016). Although the significance of decreased uric acid levels associated with SGLT2 inhibitor use has not been fully revealed, the EMPA-REG OUTCOME trial did confirm positive effects of empagliflozin on the kidney, namely via reductions in new-onset macroalbuminuria, creatinine doubling, decreased eGFR to <45 $mL \cdot min^{-1} \cdot 1.73m^{-2}$, the need for dialysis, and renal-related death (Heerspink et al., 2016). A study looking at the impacts of canagliflozin on renal events in patients with diabetes and nephropathy is ongoing and will shed more light on the

subject (Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation trial; NCT02065791).

Safety.

Hypoglycemia. Hypoglycemia can lead to confusion, shakiness, weakness, diaphoresis, loss of consciousness, seizure, and even death (Dunphy et al., 2015). Therefore, the possibility of hypoglycemia is a major consideration when weighing options for diabetes treatment. The unique mechanism of action of the SGLT2 inhibitors, being that they function independently of pancreatic beta cells and insulin, combined with maximal glucose urinary excretion of about 80 g/day (less than ½ of the filtered glucose load) results in an extremely low hypoglycemia risk with their use (Hasan, Alsahli, & Gerich, 2014). Hypoglycemia has been shown to be less prevalent in patients treated with an SGLT2 inhibitor as an add-on therapy to Metformin than those treated with add-on glimepiride (Brietzke, 2015) or sulfonylureas (Palmer et al., 2016). In fact, Palmer et al. recommended SGLT2 inhibitors as preferred add-on treatment to Metformin in those whose major adverse effect concern was hypoglycemia (2016).

Genitourinary infections. Perhaps one of the most widely discussed and reported side effects of the SGLT2 inhibitor class is the increased incidence of genitourinary infections. Early studies of SGLT2 inhibitors showed a statistically significant increase in the risk of genital infection when compared with placebo, but no statistically significant difference in the incidence of urinary tract infections, regardless of patient reports of urinary tract infections (Kawalec, Mikrut, & Lopuch, 2013). Subsequent studies, reviews, and meta-analyses have confirmed that risk for genital fungal infections is increased with the use of SGLT2 inhibitors alone or in combination therapy and that those patients with a history of genital fungal infections had even higher risk, but that these infections were generally mild and rarely (<1% of cases) led to

discontinuation of the drug (Brunton, 2015; Heerspink, 2016; Maruther et al., 2016; Qaseem et al., 2017; Whalen et al., 2015; Wilding et al., 2016). Heerspink et al. (2016) related that results of early studies showing an increase in the rates of urinary tract infections in patients taking SGLT2 inhibitors were not replicated in subsequent larger studies.

Other safety considerations. Additional side effect associations have been postulated with the use of SGLT inhibitors, including increased risk of bladder cancer, volume depletion, and fracture. According to Whalen et al., early clinical trials with dapagliflozin indicated an increase in the number of bladder tumors in the treatment group (2015). However, half of these cases were diagnosed within six months of beginning dapagliflozin and nine of the 10 patients diagnosed with bladder tumors had baseline hematuria (Whalen et al., 2015), raising the question as to whether these tumors were associated with dapagliflozin use. Bone fractures were not increased in the EMPA-REG OUTCOME trial (Heerspink et al., 2016). Additionally, Wilding et al. (2016) reported that results of an RCT that followed patients on dapagliflozin for 50 weeks showed no significant changes in bone formation or resorption markers. Finally, results of a review completed by Maruther et al. (2016) showed low or insufficient strength of evidence of risk related to fracture. Concern for volume depletion associated with diuresis from SGLT2 inhibitors has been raised and is of greatest concern in the elderly, those taking concomitant loop diuretics, and those with renal impairment (Brunton, 2015; Hasan et al., 2014; Wilding et al., 2016). Although this risk has been demonstrated in previous studies, as mentioned above, it was not duplicated in the EMPA-REG OUTCOME trial (Heerspink, 2016) and evidence of its risk in a review by Maruther et al. (2016) was insufficient or of low strength. Although SGLT2 inhibitors have not been on the market long enough to determine long-term safety, it is reassuring that individuals with “functional depletion of sodium-glucose co-transporter 2 may

not have long-term deleterious effects, at least in the individuals followed up to date" (Brunton, 2015, p. 1073).

Place in treatment

SGLT2 inhibitors are becoming front-runners as an add-on to Metformin in the treatment of type 2 diabetes. They have an innovative mechanism of action that sets them apart from other oral antidiabetic agents and the potential for positive impact on comorbid conditions that may propel them to the top of the treatment algorithm for patients who are not adequately controlled on first-line Metformin therapy. Their positive influence on cardiovascular outcomes in patients with diabetes, as evidenced in the EMPA-REG OUTCOME trial, makes a recommendation for their use as a second-line add-on therapy to ongoing Metformin preferable and, in patients with underlying cardiovascular disease or risk factors, prudent. In fact, there has already been a trend toward preferential use of SGLT2 inhibitors in patients with comorbid cardiovascular disease not at glycemic goal (Heerspink, 2016). The European Society of Cardiology has included empagliflozin in its treatment guidelines as a therapy option to decrease heart failure hospitalization in patients with diabetes (Ponikowski et al., 2016). Results of ongoing trials evaluating the impact of SGLT2 inhibition on renal end points could further augment the argument that SGLT2 inhibitors should be at the top of therapeutic algorithm.

Although SGLT2 inhibitors have the potential to largely impact outcomes in patients with type 2 diabetes, their high costs may make them unattainable to some. Additionally, patients with severe or recurrent genital mycotic infections and those at high risk for volume depletion are not good candidates for use of this class of medications. The choice of an appropriate second-line add-on therapy to Metformin should be personalized to the patient.

Learning Points

- SGLT2 inhibitors should be considered for use as preferred add-on therapy to Metformin in patients with type 2 diabetes and comorbid cardiovascular disease or cardiovascular risk factors not at glycemic goal.
- SGLT2 inhibitors may be used as an add-on therapy at any stage on the type 2 diabetes continuum due to their mechanism of action and low potential for hypoglycemia.
- SGLT2 inhibitors should be used cautiously in the elderly, with concomitant loop diuretic use, in patients with hypotension, or other predisposing risk factors for volume depletion.
- SGLT2 inhibitors should be used cautiously in patients with recurrent genital mycotic infections.
- Consider discontinuing SGLT2 inhibitors when eGFR is <30 $mL \cdot min^{-1} \cdot 1.73m^{-2}$ as they are likely to be ineffective.

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Appendix

Case Report

CC: Diabetes Recheck – saw diabetes educator last week and encouraged to come in for follow-up.

HPI: Dorothea is a pleasant 60 year-old Caucasian female who presents to the clinic today for follow-up of type 2 diabetes. She was diagnosed with diabetes approximately 10 years ago and has been well-controlled with Metformin 500 mg twice daily since diagnosis. At her appointment with the diabetic educator 3/3/2017, Dorothea revealed that her blood sugars have been elevated for the past few months, which prompted the dietician to encourage her to follow-up in clinic today.

Unfortunately, Dorothea did not bring a record of her blood glucose levels with her to this appointment; however, she reports her sugars have been consistently in the 150s to 200 range. She associates this with a less-than-optimal diet containing increased sweets and fried foods. Associated symptoms include increased fatigue for the past few months. She denies episodes of hypoglycemia. She has not experienced vision changes, including diplopia or blurred vision, headaches, lightheadedness, dizziness, syncope or near syncope, diaphoresis, numbness, tingling, sensation loss, polyphagia, polydipsia, polyuria, dysuria.

Dorothea also has a history of hypertension, for which she takes Lisinopril 20 mg daily. Her blood pressure is elevated in clinic today at 148/98. She does not check blood pressures at home or elsewhere outside of the clinic.

Medications

Metformin 500 mg twice daily

Aspirin 81 mg daily

Lisinopril 20 mg daily

Atorvastatin 20 mg daily

Multivitamin daily

Allergies

Penicillin – reaction unknown

No known latex, medication, or environmental allergies

PMH/Problem List

Diabetes type 2

Hypertension

Hyperlipidemia

Family History

Type 2 diabetes – mother and father

Social History

Married with grown children.

Works at the Simulation center at UND.

Non-smoker; no history of tobacco use.

ROS

General: Denies fever, chills, unintentional weight gain or weight loss, weakness. **Positive for fatigue.**

HEENT: Regular optometry visits. Wears corrective lenses. Denies eye pain, redness, diplopia, blurred vision, floaters, flashers.

Cardiovascular: No chest pain, palpitations, lower extremity edema

Respiratory: No cough, shortness of breath, wheeze

GI: No nausea, vomiting, diarrhea, constipation

GU: No dysuria, frequency, urgency

Endocrine: No numbness, tingling, polyuria, polydipsia, polyphagia

Physical Exam

BP 148/98 Pulse 80 Temp 98.6 F Resp 20 Wt 160 lb stated Ht 5'8" stated SpO2 not obtained

Constitutional: Patient is well-groomed, in no acute distress, does not appear ill.

HENT: Head normocephalic, atraumatic, TMs pearly gray and translucent bilaterally, external ears normal, oropharynx clear and moist, posterior pharynx without edema or exudate, soft palate rises to phonation

Eyes: PERRLA, conjunctivae without injection, no discharge, funduscopic exam reveals clear disc margins, no evidence of AV nicking, retinopathy

Neck: supple, no masses, trachea midline

Cardiovascular: Regular rhythm, S1 and S2 normal. Exam reveals no S3 or S4. No murmur, rubs, or gallop. Brisk capillary refill. No peripheral edema.

Pulmonary/Chest: Effort normal, symmetric unlabored respirations, no respiratory distress, no crackles or wheeze, no chest tenderness

GI: soft, non-tender to palpation, bowel sounds present x4, no splenomegaly

Lymphadenopathy: No retropharyngeal, submental, submandibular, preauricular, post auricular, cervical, occipital, or supraclavicular lymphadenopathy appreciated.

Neurological: Alert and oriented x 3, normal DTRs. Monofilament exam identifies no sensation abnormalities to feet bilaterally

Skin: Warm and dry, no abnormal lesions or rashes

Psychiatric: Normal mood and affect.

Lab data/Diagnostics

A1C 8.5 (up from 8.2 at last check)

UA within defined limits

CMP within defined limits

Repeat BP in clinic remained elevated

Assessment

Uncontrolled Diabetes Mellitus Type 2

Uncontrolled Hypertension

Plan

Dietary changes as discussed in patient's visit with the diabetic educator

Increase Metformin to 1000 mg twice daily

Start hydrochlorothiazide 12.5 mg daily

Continue at-home blood glucose monitoring (would ideally like some fasting, 2 hours post-meal and evening blood sugars) and contact the clinic with any episodes of hypoglycemia (BS <70)

Monitor blood pressures at home. Contact the clinic with increased dizziness, syncope or near-syncope, or low blood pressures (SBP/top number <90 or DBP/bottom number <60).

Follow-up in 2-4 weeks ; sooner with concerns

Plan to recheck Hgb A1C in 3 months

Goal A1C <7.0% (if able to achieve without hypoglycemic episodes)

If A1C level has not improved at 3 month recheck, will consider the addition of an SGLT2 inhibitor.