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A risk of renal deterioration with SGLT2 Inhibitors in normal or at risk groups with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a prevalent preventable chronic disease which arises from insulin resistance and has a variety of debilitating comorbidities including nephropathy, retinopathy, neuropathy and can predispose to or exacerbate cardiovascular disease. SGLT2 inhibitors (SGLT2i) are oral diabetic medications that act on the SGLT2 receptors in the proximal tubule of the nephron and prevent reabsorption of filtered glucose into systemic circulation. This excreted glucose results in a reduction of serum glucose and ultimately an improvement in glycated haemoglobin (HbA1c). SGLT2i should not be used as a mono-therapy and is best utilised with Metformin and/or other diabetic medications such as DPP4 inhibitors, GLP-1 or Sulfonylureas. In fact, SGLT2i can be combined with Metformin to reduce polypharmacy especially among elderly diabetic patients. HbA1c, renal function, liver function and intravascular volume should be assessed prior to initiation of SGLT2i therapy and clinicians should monitor these patients on SGLT2i after 3 months of initiation and if stable can repeat blood tests annually or where clinically indicated. Contraindications of SGLT2i therapy include recurrent urinary tract infections (UTIs), low bone mineral density and/or high risk for fracture or recurrent falls and significant renal impairment (eGFR <45 mL/min/1.73m2).

Methods: Data was randomly selected, collected and analysed retrospectively during May to June 2020 from patients who were referred to the outpatient diabetic clinics at University Hospital Kerry. 75 patients were involved in this study after applying exclusion criteria. These patients were originally referred by GP or newly diagnosed with T2DM between 2002 and 2020. Demographical information as well as medications and comorbidities were collected as well as cumulative blood results (HbA1c, renal function tests, liver function tests and lipid profile) at first presentation (baseline), prior to and after SGLT2i initiation. eGFR was calculated for each patient via MDRD eGFR calculator from renal function tests performed at baseline and prior to and after SGLT2i initiation. Data was analysed via Microsoft Excel.

Results: The majority of patients in this study were male (n=46, 61%), with an age profile of 40 years to 82 years and average age of 65 years. SGLT2i therapy was initiated on average at 62 years of age with an age profile of 37 years to 81 years. Canagliflozin was the most commonly prescribed SGLT2i (n=35, 47%), closely followed by Dapagliflozin and

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Empagliflozin (n=21, 28% and n=18, 24% respectively). 20% of patients (n=15) had a dose adjustment to improve glycaemic control and only 1 patient was changed from one SGLT2i to another. 2 patients stopped SGLT2i therapy due to oral medication intolerance and were changed to subcutaneous insulin therapy. 29% of patients (n=22) were prescribed SGLT2i combination medication with Vokanamet prescribed in 50% of these patients. 14 patients of these patients were initially started on SGLT2i combination medication with 8 patients eventually switched from SGLT2i to combination medication. 96% of all patients in this study (n=72) were using on average 2 other diabetic medications in conjunction with SGLT2i therapy. 55% of these patients were using subcutaneous medication (n=41). Metformin was the most commonly prescribed diabetic medication using SGLT2i (n=63, 84%) with. Patients were also taking on average 2 non-diabetic medications with 71% prescribed Angiotensin-converting-enzyme inhibitors (ACEi) or Angiotensin II receptor blockers (ARBs); 70% prescribed a statin; 50% prescribed aspirin; 38% prescribed a beta blocker or blood pressure medication and 8% prescribed a direct oral anticoagulant (DOAC). Each patient was found to have on average 3 comorbidities associated with T2DM with hypertension reported in 59% of patients. Neuropathy, nephropathy and retinopathy were reported in 51%, 31% and 13% respectively. Recurrent UTIs and fungal infections were reported in 5% and 3% of patients respectively. HbA1c at baseline presentation was 71mmol/mol across our patients and was 72mmol/mol prior to initiating SGLT2i therapy. HbA1c was found to have improved on SGLT2i by 5mmol/mol with an average HbA1c of 67mmol/mol reported after initiating SGLT2i therapy. Average renal function via eGFR at baseline was 81mL/min/1.73m2. It was 79mL/min/1.73m2 on average prior to initiating SGLT2i therapy and it reduced slightly to 78mL/min/1.73m2 m after introducing SGLT2i.

Conclusion: T2DM is a chronic disease with microvascular and macrovascular complications. SGLT2i are a novel oral diabetic medication used in the treatment of T2DM that increase urinary glucose excretion. It should be used in combination with other diabetic medication such as Metformin or DPP-4i, GLP-1, insulin or sulfonylureas. This study looked on the effects of SGLT2i on HbA1c and renal function among 75 patients with multiple comorbidities and medications. HbA1c improved among our patients on SGLT2i therapy which demonstrates its effect on diabetic control and comorbidities. Very few patients reported side effects from the medication and it was tolerated quite well. It is important to consider the renal function in diabetic patients if you are considering SGLT2i therapy. Our study showed a deterioration of eGFR from baseline presentation after introducing SGLT2i. This deterioration may be due to disease progression over several years or due to the effects of SGLT2i or other medication on renal function. This finding however does not warrant a dose reduction in SGLT2i. It was difficult to ascertain the exact effect of SGLT2i on renal function in this study as there are discrepancies on initiation of SGLT2i. Future studies into SGLT2i therapy should look at a larger population with an equal gender and age distribution and within a SGLT2i therapy timeframe. In conclusion, while there may be a slight deterioration in renal function, SGLT2i are a valuable asset in the treatment in T2DM.

INTRODUCTION

The aim of treating Type 2 Diabetes Mellitus (T2DM) is to increase insulin availability; improve insulin sensitivity; decrease the delivery and absorption of carbohydrate from the gut and increase urinary glucose excretion [1].

Management of T2DM in the adult population:

If HbA1c rises to 48mmol/mol, initial therapy or monotherapy should begin with lifestyle intervention (diet, weight reduction, exercise and/or Metformin) [1]. Dual therapy with Metformin and DPP-4 Inhibitors (DPP-4i) or Metformin and SGLT2 Inhibitors (SGLT2i) or Metformin and Sulfonylurea (SU) or Metformin and Thiazolidinedione (TZD) would be reasonable should the HbA1c rise to 58mmol/mol [1]. Triple therapy should be considered if HbA1c rises to or above 58mmol/mol and would consist of Metformin with DPP-4i and SU or Metformin, TZD and SU or Metformin, SU and SGLT2i or Metformin, SGLT2i and TZD or Metformin, any of the aforementioned medications and insulin therapy [1]. If triple therapy fails and the patient has a BMI greater than 35; clinicians should consider a combination of Metformin, SU and glycogen-like peptide (GLP-1). Weight loss via a multidisciplinary approach would ameliorate obesity related comorbidities [1].

SGLT2i are a novel class of oral medications that are used in the treatment of T2DM since 2013. SGLT2i increase the excretion of glucose via urine by acting on the sodium-glucose co- transporter-2 (SGLT2) receptors; therefore reducing serum glucose. The SGLT2 receptors are present on the proximal tubule of the nephron and aid in the reabsorption of filtered glucose. This ultimately results in a reduction of serum glucose and improvement of the glycated haemoglobin (HbA1c). This process is independent of insulin therefore SGLT2i do not usually cause hypoglycaemia. SGLT2i also have a promising effect on weight control and reducing blood pressure [2].

Initiating SGLT2i therapy1

Prior to initiating SGLT2i therapy; T2DM patients should have their HbA1c and intravascular volume status assessed as well as their renal function (estimated glomerular filtration rate (eGFR) and creatinine). Liver function should be assessed prior to initiation of Canagliflozin or Dapagliflozin and bone density especially in high risk patients. Monitoring of HbA1c, renal function and volume status should be performed after 3 months of initiation and can be repeated, if stable, every year or if clinically indicated. Contraindications for SGLT2i therapy include; frequent urinary tract infections (UTIs); low bone mineral density and/or high risk for fractures and falls and significant renal impairment (eGFR <45 mL/min/1.73m^2) [2].

Canagliflozin (Invokana):

The initial dose of Canagliflozin is 100mg once daily. This dose can be increased to 300mg once daily to achieve glycaemic goals. Canagliflozin should not be initiated in patients with an eGFR

<60mL/min/1.73m2. In patients tolerating Canagliflozin whose eGFR falls persistently below 60mL/min/1.73m2, the dose should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45mL/min/1.73 m2. Care

should be taken when increasing the dose in patients greater than 75 years of age. Canagliflozin is available as a combination medication with Metformin and is known as Vokanamet [3].

Dapagliflozin (Forxiga):

Dapagliflozin has a single dose regime of 10mg once daily. In general, there are no dose adjustment based on patient age however Dapagliflozin should not be initiated in diabetic patients with an eGFR <60mL/min/1.73m2 and should be discontinued with an eGFR persistently below 45mL/min/1.73m2. This SGLT2i has not been studied in severe renal impairment or end stage kidney disease. Dapagliflozin can be combined with Metformin in a combination medication called Xigduo and is given twice daily [3].

Empagliflozin (Jardiance):

Empagliflozin's initial dose is 10mg once daily and this can be increased to 25mg once daily based on glycaemic control. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m2. As with the previous SGLT2i, Empagliflozin can be combined with Metformin in a combination medication called Synjardy and is given twice daily [3].

Ertugliflozin (Steglatro):

The initial dose is 5 mg once daily and may be increased to a maximum dose of 15 mg once daily. Ertugliflozin is not recommended for patients who have persistently low eGFR (<60mL/min/1.73m2) should be discontinued if eGFR <45mL/min/1.73m2. Ertugliflozin is rarely used and has no combination with Metformin [3].

METHODS

This study was conducted at the Department of Medicine at University Hospital Kerry, Tralee, Ireland between May and June 2020. All data was randomly selected, collected and analyzed retrospectively from outpatient diabetic clinics. A total of 75 patients were involved in this study and these patients were referred by GP or newly diagnosed with T2DM from 2002 to 2020.

Inclusion criteria were all patients of our diabetic service who were diagnosed with T2DM and were commenced on SGLT2i. Exclusion criteria were patients on lifestyle interventions alone and patients on single, double, triple or insulin therapy without commencing SGLT2i at any stage of their management.

Demographics such as age and gender were collected as well as documented medications (diabetic and non-diabetic) and documented comorbidities (hypertension, nephropathy, retinopathy etc.). HbA1c, renal function, lipid and liver profile values were obtained as a cumulative through our online laboratory service. Blood results were reviewed at first presentation to diabetic clinic (baseline) and prior to and after initiation of SGLT2i therapy. eGFR was calculated for every patient via MDRD eGFR calculator [4]. Data analysis was performed via Microsoft Excel.

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