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SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: A systematic review and meta-analysis

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ABSTRACT

Background: Sodium–glucose co-transporter 2 (SGLT2) inhibitors may have renal protective effects in people with impaired kidney function. We assessed the use of SGLT2 inhibitors in people with type 2 diabetes with or without renal impairment [defined as estimated glomerular filtration rate (eGFR) of ≥30 and <60 ml/min/1.73 m^2 and/or UACR > 300 and ≤5000 mg/g] by conducting a systematic review and meta-analysis of available studies.
Methods: Randomised controlled trials (RCTs) were identified from MEDLINE, EMABASE, Web of Science, the Cochrane Library, and search of bibliographies to March 2017. No relevant observational study was identified. Summary measures were presented as mean differences and narrative synthesis performed for studies that could not be pooled.
Results: 42 articles which included 40 RCTs comprising 29,954 patients were included. In populations with renal impairment, SGLT2 inhibition compared with placebo was consistently associated with an initial decrease in eGFR followed by an increase and return to baseline levels. In pooled analysis of 17 studies in populations without renal impairment, there was no significant change in eGFR comparing SGLT2 inhibitors with placebo (mean difference, 0.51 ml/min/1.73 m^2; 95% CI: −0.69, 1.72; $p = 403$). SGLT2 inhibition relative to placebo was associated with preservation in serum creatinine levels or initial increases followed by return to baseline levels in patients with renal impairment, but levels were preserved in patients without renal impairment. In populations with or without renal impairment, SGLT2 inhibitors (particularly canagliflozin and empagliflozin) compared with placebo were

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associated with decreased urine albumin, improved albuminiuria, slowed progression to macroalbuminuria, and reduced the risk of worsening renal impairment, the initiation of kidney transplant, and death from renal disease.

Conclusions: Emerging data suggests that with SGLT2 inhibition, renal function seems to be preserved in people with diabetes with or without renal impairment. Furthermore, SGLT2 inhibition prevents further renal function deterioration and death from kidney disease in these patients.

1. Introduction

There is a large and growing burden of diabetes globally. In 2013, 382 million people had diabetes and this number has been projected to increase to 592 million by 2035 [1]. With increasing life expectancy and prevalence of type 2 diabetes, complications and deaths attributable to diabetes will also increase, especially if there is no concomitant improvement in the health system for its early management [1]. Chronic kidney disease (CKD) is a common complication in people with type 2 diabetes [2] and may in some cases progress to end-stage renal disease, which requires dialysis and/or kidney transplant which are associated with high healthcare costs [3–5]. Indeed, a recent population-based study showed that the costs associated with the treatment of end-stage renal disease in patients with type 2 diabetes was ten times that of type 2 diabetes patients without renal failure [5].

The kidneys are involved not just in the pharmacokinetic processing of many antidiabetic agents [6–9], but also in the mechanisms of action of some classes of antidiabetic drugs [10]. Therefore, prescribing antidiabetic drugs in patients with diabetes and CKD can be very challenging, with special concerns regarding safety and efficacy and the need for appropriate dosage adjustment according to the renal function. For patients with type 2 diabetes and CKD, there are limited treatment options for glycaemic control.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, are novel therapeutic agents for the treatment of type 2 diabetes and work by inhibiting glucose reabsorption and induce excretion of glucose in the urine, thereby reducing circulating plasma glucose levels [11]. Their mechanisms of action are independent of insulin action or beta-cell function and their use is associated with reductions in HbA1c levels, weight and systolic blood pressure [10]. Data from phase III trials suggest that SGLT2 inhibitors might achieve their beneficial effects without having significant adverse effects. Treatment with canagliflozin was shown to be associated with decreased albuminuria and an early decrease in estimated glomerular filtration rate (eGFR) [12,13]. Yale et al. reported that a lower proportion of participants in the canagliflozin 100 and 300 mg groups progressed from normoalbuminuria to micro- or macro-albuminuria, or from micro- to macro-albuminuria compared with those in the placebo group [13]. In the CANagliflozin CardioVascular Assessment Study (CANVAS), there were significant reductions in albuminuria and the albumin-to-creatinine ratio for canagliflozin 100 mg and 300 mg doses, compared with placebo [12]. For nearly 2 decades, the use of Renin-Angiotensin-Aldosterone system (RAAS) inhibition has been employed in the management of diabetes to reduce the rate of progression of diabetes nephropathy [14,15]. The kidney plays a key role in modulating glucose levels by mediating the reabsorption of glucose back into the plasma, after filtration of the blood. Similarly, SGLT2-inhibitors cause vaso-constriction of the afferent arterioles, thus decreasing the hyper-filtration in the glomerulus. This then can lead to a decrease in the rate of progression of proteinuria [8]. These new type 2 diabetes drugs may therefore offer an alternative option for renal protection. Since the mechanism of renal protection of SGLT2 inhibitors seems to occur independently of their glycaemic controlling effect, it is plausible that their effect on prevention of deterioration of renal function could be maintained; even when they are used in patients with impaired renal function, where they are usually deemed not to be effective for glucose control. Currently SLGT2 inhibitors are only licenced for use in glycaemic control and hence contra-indicated in people with eGFR less than 45 ml/min/1.73 m^2. In the absence of treatment options for the prevention of deterioration of renal impairment other than RAAS inhibition, the use of SGLT2 inhibitors show some promise in this area. To our knowledge, the only RCT designed to assess whether an SGLT2 inhibitor compared with a placebo, has a renal protective effect in participants with type 2 diabetes mellitus, chronic kidney disease and macroalbuminuria, is the "Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) study". However, this study is not due to be completed until 2019. (ClinicalTrials.gov Identifier: NCT02065791). There are currently no systematic reviews or meta-analysis of RCTs on this subject. In this context, we aimed to pool available interventional evidence in one updated systematic meta-analysis. Our aim was to determine if the use of SGLT2 inhibition prevents further renal function deterioration in people with type 2 diabetes with or without renal impairment.

2. Methods

2.1. Data sources and search strategy

This review was conducted using a predefined protocol and in accordance with PRISMA (Appendices 1). We sought studies published before March 06, 2017 (date last searched) using MEDLINE, EMBASE, Web of Science, and the Cochrane electronic databases. The computer-based searches com-