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SGLT-2 Inhibitor: A Unique Antidiabetic in Type 2 Diabetes Mellitus

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INTRODUCTION

Type 2 diabetes is a progressive metabolic disorder characterised by insulin insensitivity, relative insulin deficiency resulting hyperglycaemia.[1]The pharmacotherapy for type 2 diabetes until the last decade only consisted of biguanides, sulphonylureas, and insulin. Rapid increase in the number of blood glucose-lowering agents which have become available including thiazolidinediones (in 2000), dipeptidylpeptidase-4 (DPPIV) inhibitors (in 2007) and glucagon-like peptide-1 (GLP-1) mimetics (in 2007).[1] Despite of glucose lowering effect approximately 85% of patients with T2DM are overweight or obese, and failure to lose even part of the excess weight and continual weight gain are powerful forces against acceptable glycaemic control.[2] To develop agents that control glycaemia whilst also inducing weight loss or preventing further weight gain was one of the main challenges of the past decade of pharmaceutical innovation.

It is now well documented that the kidney has a significant role in glucose homeostasis under both physiological and pathological conditions.[3]The major renal mechanisms affecting glucose metabolism are gluconeogenesis and reabsorption of filtered glucose.The facilitated glucose transporters (GLUTs) and the sodium-coupled glucose co transporters (SGLTs) control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier, and peripheral tissues. SGLTs mediate the transport of glucose against a concentration gradient by cotransport with sodium.[3] This review will focus on the SGLT inhibitors benefits and their potential benefits.

SGLT2-INHIBITORS MECHANISM OF ACTION

Sodium-glucose co-transporter-2 inhibitors work by inhibiting SGLT2 in the proximal convoluted tubule, to prevent reabsorption of glucose and facilitate its excretion in urine. As a result plasma levels fallleading to an improvement in all glycemic parameters. This mechanism of action is independent of the actions of insulin, unlike the actions of other oral anti-glycemic agents. Thus, there is minimal potential for hypoglycemia, and no risk of overstimulation or fatigue of the beta cells. SGLT2I efficacy is reduced in persons with renal impairment as their mode of action relies upon normal renal glomerular-tubular function.[4]

SGLT2 BENEFITS

All SGLT-2 inhibitors seem to have similar benefits and risks within the class, including significant reductions in HbA1c and fasting glucose. The most interesting, perhaps, is its ability to positively influence other significant factors, including body weight, blood pressure, lipids and uric acid. Older agents have typically been filled with unfavorable effects on body weight (SU, thiazolidinediones, insulin), on the cardiovascular system (SU and TZDs) and lipids (TZDs). There are still unanswered questions about the possible risk for cancer, the durability of these agents, and how its favorable metabolic profiles will influence the risk of micro and macro vascular disease. The SGLT2 inhibitors have an independent action of insulin, are effective to promote weight loss, have a low incidence of hypoglycemia, complement the action of other anti-diabetic agents, and can be used regardless of diabetes duration.[6]

Findings from this post hoc analysis by Kumar KM et al., of pooled Phase 3 studies demonstrated that canagliflozin provided glycemic improvements and reductions in body weight and BP in patients with T2DM from India. The reductions in body weight were consistent with those observed with canagliflozin in the overall population. As canagliflozin lowers blood glucose through an insulin-independent mechanism, the glycemic improvements and reductions in body weight and BP provided by canagliflozin may be particularly beneficial in treating patient populations that generally have a higher prevalence of insulin resistance and beta-cell dysfunction.[7] Results of the aforementioned studies is shown in figure 1 below.[7]

The EMPA-REG trial disclose cardiovascular safety study of empagliflozin, assessed the effect of two doses of empagliflozin—10 mg and 25 mg—on cardiovascular events in patients who were being treated with standard care for type 2 diabetes over a median of 3.1 years. Empagliflozin prevented more than one-third of CV deaths, with a 38% relative reduction. A total of 3.7% of empagliflozin-treated subjects experienced CV death vs 5.9% for placebo: HR=0.62 (95% CI: 0.49, 0.77); P<0.001.[8] Empagliflozin was associated with slower progression of kidney disease than was placebo when added to standard care in patients with type 2 diabetes who were at high risk for cardiovascular events. Empagliflozin was also associated with a significantly lower risk of clinically relevant renal events as shown in figure 3 below.[9]

A recently published study on canagliflozin suggested that Canagliflozin slowed the progression of renal disease over 2 years in patients with type 2 diabetes, and canagliflozin

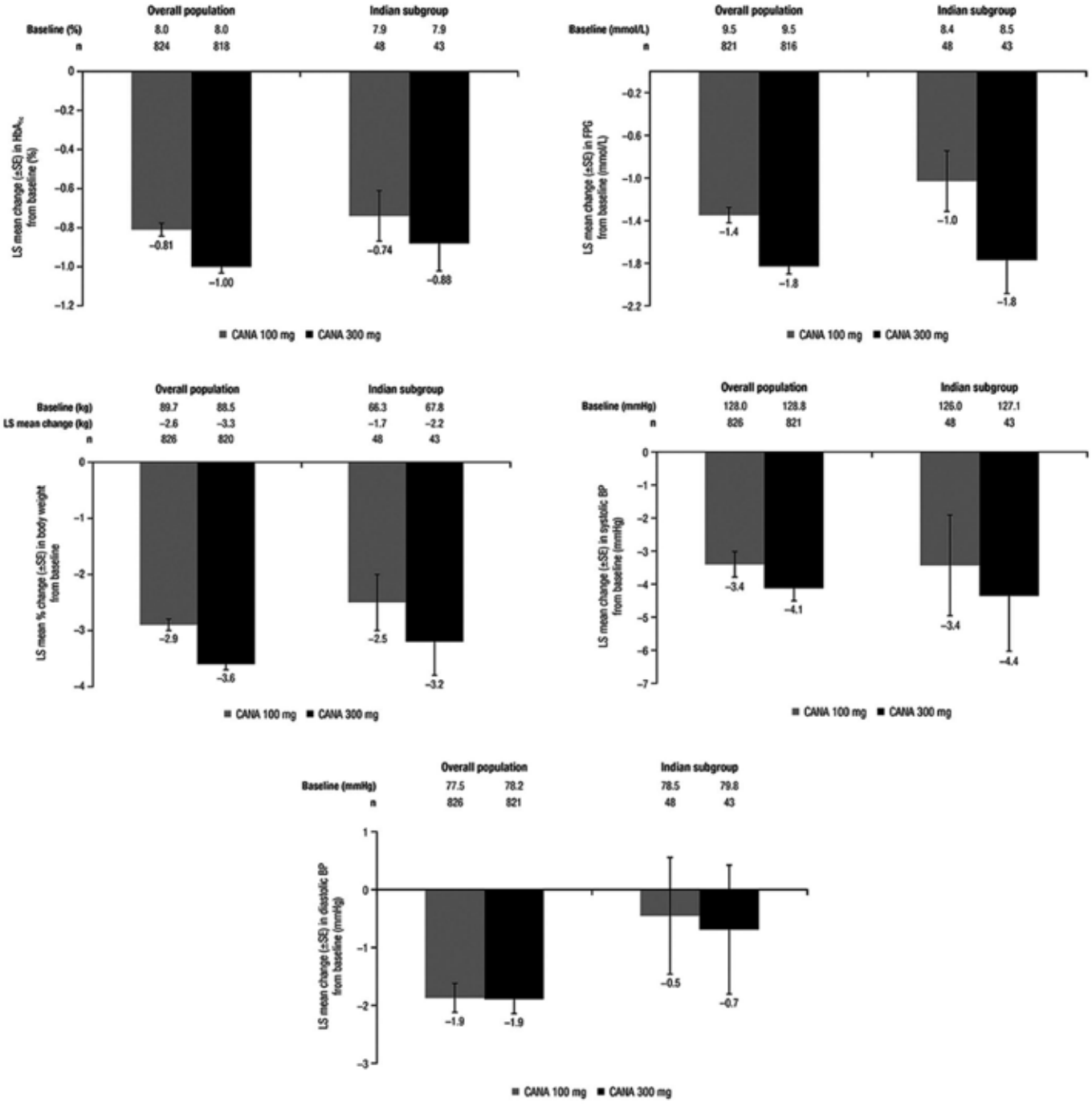


Fig. 1: Changes from baseline in (a) HbA1c, (b) FPG, (c) body weight, (d) systolic BP, and (e) diastolic BP in the overall population and in the Indian subgroup at week 52 (Population 1). FPG: Fasting plasma glucose, BP: Blood pressure, CANA: Canagliflozin, LS: Least squares, SE: Standard error

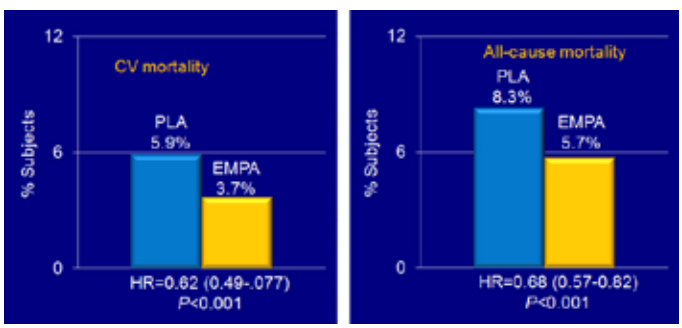


Fig. 2:

may confer renoprotective effects independently of its glycemic effects.

A recent meta-analysis suggested that CV benefit is a class effect of SGLT2 inhibitors. SGLT-2 inhibitors as a class significantly reduced cardiovascular mortality (MH-OR [95 % CI] 0.43 [0.36–0.53], p\0.001). There are ongoing CV outcome studies on other SGLT2 inhibitors namely CANVAS (Canagliflozin Cardiovascular Assessment Study) and DECLARE TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) which have a different patient population consisting of a mixture of patients with established CAD and patients with CV risk factors. These

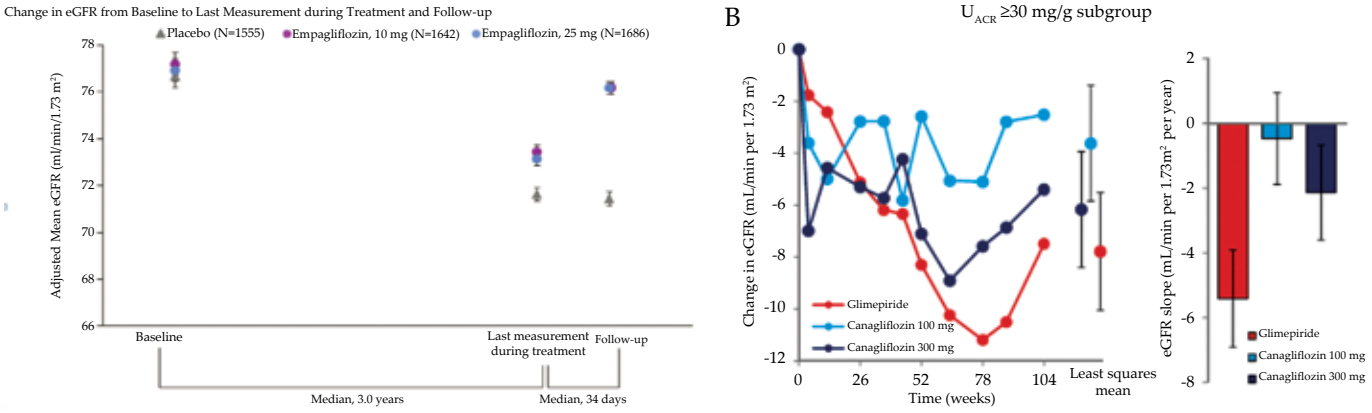
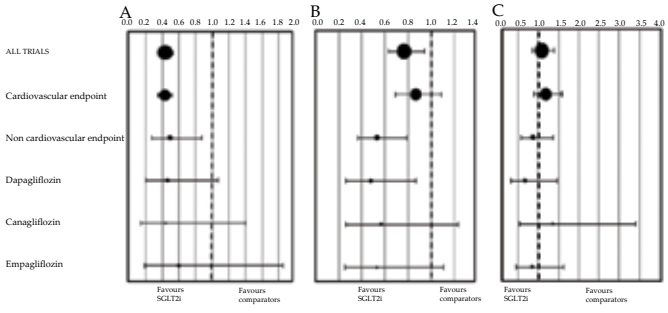


Fig. 3: Renal Function over time with Empagliflozin and Canagliflozin



	MH-OR [95%, CI] p	MH-OR [95%, CI] p	MH-OR [95%, CI] p
All trials:	0.43[0.36-0.53] <0.001	0.77[0.63-0.94] 0.010	1.09[0.86-1.38] 0.50
CV endpoint	0.43[0.35-0.52] <0.001	0.87[0.69-1.09] 0.23	1.19[0.89-1.58] 0.23
Non CV endpoint	0.49[0.27-0.87] 0.016	0.53[0.36-0.79] 0.002	0.88[0.57-1.36] 0.57
Dapagliflozin	0.46[0.20-1.07] 0.071	0.48[0.26-0.87] 0.017	0.68[0.31-1.46] 0.32
Canagliflozin	0.44[0.14-1.40] 0.16	0.57[0.26-1.25] 0.15	1.36[0.54-3.40] 0.51
Empagliflozin	0.60[0.19-1.85] 0.37	0.53[0.25-1.11] 0.093	0.85[0.45-1.62] 0.63

Fig. 4 : Cardiovascular mortality (a), myocardial infarction (b), and stroke (c) considering all randomized clinical trials with and without cardiovascular endpoints. SGLT2i sodium-glucose transporter 2 inhibitors

trials are going to provide broader clinical insights as EMPA-REG OUTCOME study had included only patients with established CAD.

CONCLUSION

In summary, SGLT-2 inhibitors are an exciting and promising class of drugs for the treatment of type 2 diabetes. They provided glycemic improvements and reductions in body weight and BP, slower progression of kidney disease, significantly lower rates of the primary composite cardiovascular outcome and of deathwith some studies suggesting renoprotectionand are generally well-tolerated in patients with T2DM.

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