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Role of Combination Therapy with SGLT2 Inhibitor with Metformin as Initial Treatment for Type2 Diabetes-Advantages of Oral Fixed Drug Pill Like Empagliflozin/ Metformin in Patients with Cardiovascular and Renal Risk-A Short Communication

Dr. Kulvinder Kochar Kaur, M.D.,[1]* Dr. Gautam Allahbadia M.D.(Obstt & Gynae), D.N.B,[2] Dr. Mandeep Singh M.D.DM.(Std)(Neurology)[3]

[1]Scientific Director, Dr. Kulvinder Kaur Centre For Human Reproduction, 721,G.T.B. Nagar, Jalandhar-144001, Punjab, India.

[2]Scientific Director, Ex-Rotunda-A Centre for Human reproduction, 672, Kalpak Garden, Perry Cross Road, Near Otter's Club, Bandra (W)-400040, Mumbai, India.

[3]Consultant Neurologist, Swami Satyanand Hospital, Near Nawi Kachehri,Baradri, Ladowali road, Jalandhar, Punjab. India.

kulvinder.dr@gmail.com

***Corresponding Author:** Dr. Kulvinder Kochar Kaur, Scientific Director, Dr. Kulvinder Kaur Centre For Human Reproduction, 721,G.T.B. Nagar, Jalandhar-144001, Punjab, India.*

Abstract

The incidence of Type 2 Diabetes is increasing worldwide, associated with obesity, so much so that the term diabesity got coined. Not only is the incidence increasing but both morbidity and mortality are increasing worldwide. Thus it is empirical to treat T2DM efficiently so that the cardiovascular (CV) and renal problems get taken care of. All the ADA/AACE/ACE recommend treating with a combination therapy in patients having a high Hb A1c. The preferred drugs has been the initial metformin and recent multiple trials and studies have shown the superiority of the sodium glucose cotransporter 2(SGLT2) inhibitor of which empagliflozin along with metformin has been tried in fixed dose combination, whose advantages are not only that they take care of T2DM but have simultaneous weight reducing, blood pressure reducing, increased compliance along with individualization of therapy for the patients having a risk of major adverse CV event as tested by the EMPA-REG-OUTCOME in 7020 patients along with further corroborated with more studies. Thus simultaneous control ofT2DM, BP, weight, CV outcomes and renal effects makes a combination of empagliflozin 10 or 25mg in combination with metformin, both having complementary roles and need to be the initial treatment of choice in a fixed dose pill ,making it easier for the patient to need just one tablet. In 2016 FDA has also recommended the use of this for this group of patients having major risk of CV events.

Keywords: *T2DM; SGLT2 Inhibitors; metformin; empagliflozin; FDA; CV event*

Conventionally a stepwise approach has been used to treat type 2 diabetes mellitus (T2DM), like initial lifestyle interventions and metformin being the first line therapy, followed by addition of 2nd line therapy once optimal glycaemic control is not achieved. Yet, an alternative more intensive approach remains an initial combination therapy. There is a disparity in current guidelines regarding patients glycated haemoglobin (Hb A1c) for which initial combination therapy should be considered as per the American Diabetes Association (ADA) and European Association for the Study of Diabetes(EASD)if Hb A1cis >1,5% above the patient's target or is indicated as per American s Association Of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) if Hb A1cis >7.5%[1,2]. In favour for initial combination therapy instead of

metformin monotherapy proponents argue that this avoids clinical inertia along with potential for more pronounced and earlier improvement in glycaemic control, which might =>a legacy effect [3,4]. In the UK Prospective Diabetes Study (UKPDS), especially newly diagnosed Type2 diabetes mellitus (T2DM) participants were randomized to intensive therapy achieved a lower Hb A1c as compared to participants randomized to conventional therapy (7,0% versus 7.9%)[5]. Once the study ended, this difference in Hb A1c between the 2 groups was lost by one year; though after 10yrs of follow up, the intensive therapy group had a lower risk of myocardial infarction along with T2DM related death as compared to conventional therapy[6].

Sodium–glucose cotransporter 2(SGLT2) inhibitors, remain an attractive choice for starting initial combination therapy with metformin. Their mechanism of action is insulin –independent ,i.e. by increasing the urinary excretion of glucose[7]. Along with that weight reduction and lowering of blood pressure(BP) occurs in contrast to placebo[7]. Empaglifozin, canaglifozin, and dapaglifozin have been found to decrease the risk of hospitalization from heart failure and stroke in people having T2DM with established cardiovascular disease or multiple cardiovascular risk factors significantly [8-10]. A decrease in risk of total outcome of cardiovascular death, myocardial infarction and stroke in people with T2DM and established atherosclerosis, cardiovascular disease (CVD) with SGLT2 inhibitors use was obvious in these cardiovascular outcome trials [11]. Earlier meta-analysis compared initial combination therapy of various antihyperglycaemic agents with metformin to metformin monotherapy [12]. In this meta-analysis only one SGLT-2 Inhibitor, dapaglifozin got included in the meta-analysis. Further the efficacy measures only included glycaemic control, with effects on bodyweight and BP were not examined. Recently Cai et al [13] conducted a meta-analysis where they examined initial combination therapy which included SGLT2 inhibitor and metformin in treatment naïve T2DM patient. But all treatment groups from each trial of combination SGLT2 inhibitor and metformin were not included, with a discrepancy between number of subjects included in the efficacy and safety assessments. Moreover dose response relationships were not included. Empaglifozin is an SGLT 2 Inhibitor which is in common with other agents in this class and decreases the elevated blood glucose levels by inhibiting SGLT2, that is the main transporter needed for reabsorption of glucose from the glomerular flltrate and hence increases urinary excretion of glucose[14-16]. In contrast although the mechanism of action of metformin is not fully understood, its antihyperglycaemic effects are thought to arise from the suppression of hepatic gluconeogenesis[17]. Since both agents have complementary mechanism of action [18] these 2 drugs have the potential to offer improved glucose control compared with that achieved with individual agents. An oral fixed dose, single pill combination of empaglifozin and metformin is also available for patients having T2DM in a range of dose combinations that may help in individualizing therapy [19]. This approach might decrease the burden of pill for patient and hence=>simplified medical costs as compared to the ''loose –dose'' combination in patients with T2DM[20]. Ultimately this improved adherence to therapy might ultimately help to achieve better glycaemic control in T2DM[20,21]. Moreover, with increasing evidence that supports initial combination therapy initially for T2DM patient irrespective of the HbA1c levels given in current treatment guidelines[20], or the use of early intensification therapy [22,23], suggests an increasing role for these fixed dose combinations in management of T2DM. In 2016, a new indication for empagliflozin was added by the Food and Drug Administration), namely to decrease the risk of major adverse cardiovascular (CV)events with T2DM in patient and CV disease (CVD) [20], once the EMPA-REG OUTCOME(EMPA glozin Removal of Excess Glucose: cardiovascular OUTCOME Event Trial in T2DM Patients) (NCT011131676) got published[24]. EMPA-REG OUTCOME was a randomized, double blind trial which assessed the effect of empagliflozin (10mg or25mg/day) vs placebo, added to standard care, on CV outcomes in 7020 patient with T2DM and existing CVD over a median follow up of 3.1 yrs. Most patient in the empagliflozin group(74%) were also receiving background metformin. Treatment with empagliflozin was associated with 14% relative risk reduction (RRR) in CV death, nonfatal myocardial infarction, or nonfatal stroke, 38% RRR in CV death; and 32% RRR in death of any cause[25]. RR for hospitalization for

heart failure was also decreased by 35%[25]. Basic mechanisms for the CV benefits of empagliflozin are not understood fully, but changes in arterial stiffness, alterations in cardiac oxygen demand, cardiorenal effects, decrease in albuminuria and uric acid, and the established effects of SGLT2 inhibitors like lowering glucose, weight and BP have been proposed[25]. The EMPA-REG OUTCOME trial also showed microvascular benefits of empagliflozin in the sense they slow down the progression of kidney disease (defined as incidence of worsening nephropathy)vs placebo when added to standard care [26]. Both short and long term benefits, in terms of significant decreases in urinary albumin-to-creatine ratio, in patients with T2DM and established CVD was found on exploring the findings of this trial[27]. These findings are reflected in current guidance for T2DM management issued by ADA[28] and AACA/ACE[29] that refers to the possible benefits of empagliflozin on cardiac and renal outcomes.

Watching the findings of EMPA-REG OUTCOME [25], role of empagliflozin in the treatment was evaluated in a range of treatment combinations and considered for use in earlier stages of T2DM. Since metformin[30-33], has also been associated with improvements in CV outcomes, combination therapy with empagliflozin might also confer CV benefits in patients with DM. Considering the potential benefits of dual therapy with empagliflozin and metformin in patients with T2DM, besides frequent requirement for dual therapy Goldman 2018 reviewed on the efficacy and safety of empagliflozin/metformin combination therapy. They found that combination of empagliflozin/metformin offers the potential to improve glycemic control in T2DM and decreases body weigh patients and BP, vs each agent individually, with a management risk profile. Thus this combination could be suitable for patients with T2DM who are inadequately controlled by metformin, especially in patients who would benefit from modest reductions in BP and body weight who have risk factors for CV diseases or reducing renal function. Further empagliflozin/metformin is also available as a single–pill combination that has the potential to provide a simplified regimen and could =>improved clinical outcomes compared with administration of individual tablets.[34].

Further Milder et al compared the efficacy and safety of i) sodium–glucose cotransporter2 inhibitor combination therapy in treatment naïve T2DM adults, ii) initial high and low dose SGLT2 inhibitor combination therapy. They used randomized controlled trials(RCT's) of initial SGLT2 combination therapy. Mean differences (MD) for changes from baseline (Hb A1c, weight, BP) after 24-26weeks of treatment and relative risks (RR, safety) were calculated using a random effects model. Risk of bias and quality of evidence was assessed. In 4RCT's (n=3749) there was moderate quality of evidence that SGLT2 inhibitor /metformin combination therapy resulted in a greater reduction in Hb A1c(MD(95%CI);-0.55% (-0.67,-0.43) and weight (-2.00Kg(-2.34,-1.66)) compared with metformin monotherapy, and a greater reduction in Hb A1c(-0.59(-0,72,-0.46) and weight (-0.57kg(-.0.89,-0.25) compared with SGLT2 inhibitor monortherapy. The high dose SGLT2 inhibitor / metformin combination resulted in similar Hb A1c but more weight reduction ;(-0.47kg(-0.88,-0.6) than the low dose combination therapy. The RR of genital infection with combination therapy was 2.22(95%CI-1.46, 3.40) compared with metformin and SGLT2 monotherapy. Thus conclusions drawn were initial SGLT2/metformin combination therapy has glycaemic and weight benefits compared with either agent alone and appears safe. High dose SGLT2 inhibitor / metformin combination therapy appears to have modest weight, but no glycaemic benefits compared with the low dose combination therapy[35].

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