Efficacy And Safety Of Canagliflozin Among Patients With Type 2 Diabetes Mellitus: A Systematic Review And Meta-Analysis

**INTRODUCTION**

The Global Diabetes Atlas 2019 shows that 357 million people have diabetes and the incidence of type 2 diabetes mellitus (T2DM) is rising across the world.

**Pharmacotherapy of T2DM should be patient-centered, considering aspects like efficacy, side-effects, costs and the need for glycemic control.**

- American Diabetes Association guidelines recommend metformin as the preferred first drug of choice with lifestyle modifications for patients with T2DM.

**This chronic progressive disease may require continuous augmentation of treatment with insulin or non-insulin therapy to achieve recommended glycemic goals.**

- Canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor was approved by the FDA for use in the management of T2DM, thus mainly responsible for renal glucose reabsorption.

**Canagliflozin lowers renal threshold for glucose reabsorption and thus helps in lowering plasma glucose levels.**

- Renal threshold is the plasma glucose concentration below which almost all the filtered glucose is not reabsorbed above which glycosuria occurs.

- The efficacy of canagliflozin has been demonstrated as compared to placebo, but there are concerns about the adverse events like genital mycotic infections, urinary tract infections and hypokalemia etc. have to be monitored closely to predict the results of trials studying the efficacy and safety of canagliflozin in combination therapy and with a duration of at least 26 weeks.

**OBJECTIVE**

To assess the efficacy and safety of canagliflozin in combination therapy among patients with inadequacy controlled type 2 diabetes mellitus.

**METHODS**

- **Inclusion criteria:**
  - Randomized controlled trials or quasi-randomized trials with at least 26 weeks of duration were included.
  - Patient characteristics: T2DM patients, in the age group 18-80 years with inadequate glycemic control with routine hypoglycemic agents, diet and exercise.
  - Type of interventions: Addition of canagliflozin (100 mg or 300 mg) in earlier regime of oral antihyperglycemic agents.
  - Primary outcomes: Mean change in HbA1c levels at 26 weeks; mean change in fasting plasma glucose (FPG) levels at 26 weeks; incidence of genital infections at 26 weeks.

- **Exclusion criteria:**
  - Proportion of patients achieving HbA1c levels <7%; mean change in body weight mean changes in HbA1c levels; incidence of urinary tract infections at 26 weeks.

- **Search methods for identification of studies:**
  - Relevant trials regardless of language or publication status (published, unpublished) were included.

- **Databases:** Two reviewers independently screened the databases, Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library, MEDLINE, EMBASE, LILACS and IndMed till 8th January 2015. Search terms: canagliflozin, type 2 diabetes mellitus.

- **Data collection and analysis:** Two authors independently extracted data using a specifically developed data extraction form.

- **Assessment of risk of bias in included studies:** Two authors independently assessed the risk of bias using the Cochrane risk of bias form. Six components were assessed. Judgments were categorized as either "low", "high", or "unclear" risk of bias.

- **Data synthesis:** Analyses were performed using Review Manager (RevMan) of Cochrane collaboration.

- **Secondary outcomes:**
  - Glycemic control with anti-hyperglycemic agents, diet and exercise.

- **Assessment of heterogeneity:** The statistical heterogeneity was analyzed by looking at the forest plots for overlapping CIs, applying the Chi² test (P < 0.10 considered statistically significant) and I² (I² > 50% considered substantially significant) for continuous data.

- **Quality assessment:** We performed the subgroup analysis and investigated the heterogeneity: We performed the subgroup analysis and investigated the heterogeneity.

**RESULTS**

- Literature search was conducted up to January 2015 and 124 references identified (Figure 1). After excluding the duplicate reports, 55 records were screened and their 26 were excluded. Then 29 studies were evaluated at eligibility. All studies were published in English.

- **Included studies:**
  - Five randomized double blind clinical trials enrolling 1585 patients were included in the quantitative analysis. All trials had multinational design.
  - All studies had compared canagliflozin (100 mg and 300 mg) once daily in combination therapy with placebo or sitagliptin. All these three had measured HbA1c, LGs and BMI levels, and conducted adverse event monitoring for genital infections; were of at least 26 weeks of duration and patients were in the age group of 18-80 years.

- **Efficacy of intervention:**
  - Canagliflozin led to a significant decrease in HbA1c levels (MD -0.77 [95% CI -1.05, -0.50, p<0.001]). LGs levels (MD -2.01 [95% CI -2.34, -1.68, p<0.001]) and body weight (MD -2.50 [95% CI -2.99, -2.01]) after 26 weeks as compared to placebo (Analysis 1.1-1.3).

- **Subgroup analysis:** The risk of occurrence of urinary tract infections (RR 1.33 [95% CI 0.80, 2.91, p=0.27]) and genital mycotic infections among males (RR 1.06 [95% CI 0.89, 1.27]) remained lower in the canagliflozin arm as compared to placebo arm (Analysis 1.4-1.6).

**DISCUSSION**

- The association of inadequate glycemic control with the occurrence of diabetic complications necessitates appropriate control of plasma glucose levels. Canagliflozin is an addition to the armamentarium of oral antihyperglycemic agents to be available for patient centered management.

**CONCLUSION**

- Canagliflozin is significantly more efficacious than placebo in maintaining glycemic control when used in combination therapy. The incidence of urinary tract infections, pyelonephritis, polyuria, polydipsia, dysuria and hypertension is not significantly more than placebo. Moreover, the occurrence of genital mycotic infections is significantly more with canagliflozin as compared to placebo.

**REFERENCES**

5. Taylor SR, Harris KF. Pharmacotherapy 2013;33:844-850