ISSN No:-2456-2165

Prevention of Cardiovascular Events with Sglt2 Inhibitors in Type 2 Diabetes Mellitus: A Meta Analysis of Randomized Controlled Trials

Mrs.BHARATHI PRIYA.K,M.Pharm.,(Ph.d)
Head of the Department –Pharmacy Practice
C.L.BAID METHA COLLEGE OF PHARMACY
(AFFILIATED TO THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY)
Chennai-600097, India
DISHIGA AJI, MONIKA SHREE.T, BERNISHA ROSE.M.V, ESLI JONES.J
PHARM.D INTERNS
C.L.BAID METHA COLLEGE OF PHARMACY
(AFFILIATED TO THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY)
Chennai-600097, India

Abstract:-

***Background*- In India, it has been figured out that 1 in 6 adults live with Diabetes. India ranks number 2 among the top 10 leading countries with Diabetes and it is reckoned as the diabetes capital of the world. Type 2 diabetes is the chief risk factor to cause cardiovascular complications which leads to increase in mortality and morbidity rates. In recent years, the development of newer class of antidiabetic agents such as SGLT2 inhibitors have been proven to be favourable for diabetic patients and many number of theories have been put forwarded to proclaim the cardioprotective potential of SGLT2 inhibitors. In our study we assessed the cardiovascular outcomes of SGLT 2 inhibitors in Type 2 Diabetes Mellitus patients with Cardiovascular risk.**

***Method*- We conducted a meta analysis based on multicentric randomized placebo- controlled trials of three SGLT2 Inhibitors namely Empagliflozin,Dapagliflozin and Ertugliflozin.The statistical analysis was done using Revman statistical software and risk ratios with 95% confidence interval were obtained.**

***Results*- A total of 32,426 participants with type 2 diabetes were included in our Meta analysis. We identified that the SGLT 2 inhibitors can potentially protect the Type 2 DM patients against the cardiovascular events like hospitalization for Heart failure and 3 point MACE.**

***Abbreviations*–** DM=Diabetes mellitus, CVD=cardiovascular disease,SGLT2=Sodium–Glucose linked Cotransporter 2,MACE=major adverse cardiovascular events,HHF=hospitalization for heart failure,RR= risk ratio or relative risk ,PICO = Patient/population I=Intervention C=comparator O=outcomes,PRISMA= preferred reporting items for systematic reviews.

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder that results from interruption in insulin secretion, insulin action or dysfunction of pancreatic β-cell. Diabetes is among the top 10 leading cause of death in the world. It is a serious threat to global health and Type 2 Diabetes accounts for 90% of all diabetes cases.

Based on the recent data from World Health Organization (WHO), it has been measured that Diabetes ranks number 9 among the top 10 chief causes of global deaths. It is projected that by the year 2045, approximately 700 million adults would be diagnosed with Diabetes According to the global diabetes data report, Diabetes causes increase in the risk of premature mortality. Furthermore, IDF estimated over 4 million deaths a year due to Diabetes and its complications[1].

Hyperglycemia is the predominant risk factor to cause microvascular complications and cardiovascular disease. There is a two – three fold higher risk of cardiovascular events to occur in individuals diagnosed with Type 2 Diabetes mellitus. It is recorded that cardiovascular disease is the foremost cause of mortality in Type 2 Diabetes mellitus patients and among the CV events cardiovascular death accounts for 80% of the mortality in Type 2 DM[2].

The novel antidiabetic drugs involved in the assessment of cardiovascular safety includes GLP1 agonist (exenatide, liraglutide), DPP-4 inhibitors such as sitagliptin, saxagliptin and SGLT2 inhibitors-selective sodium-glucose linked transporter 2 inhibitors. SGLT2 inhibitors are the new class of oral antihypoglycemic agents that are approved by the U.S FDA is used in the management of Type 2 Diabetes mellitus.

SGLT2 is a glucose transporter found in the proximal tubule. It plays a major role in glucose reabsorption.SGLT2 inhibitors are the agents that stimulates the renal excretion of glucose by acting on proximal convulated tubule and thereby

ISSN No:-2456-2165

reduces the excessive blood glucose levels in patients with Type 2.. The SGLT2 inhibitors decreases the reabsorption of glucose and lower the renal threshold for glucose. Drugs that comes under this class includes Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliglozin. SGLT2 inhibitors have found to be effective in treating diabetic patients with cardiac disorders. The most plausible mechanisms by which SGLT2 inhibitors acts as cardioprotective are as follows :- Change in cardiac energy metabolism, improves cardiac preload, reduces vascular stiffness, epicardial fat, osmotic diuresis and reduces oxidative stress. Certain cardiovascular outcome trials have put forward that SGLT2 inhibitors (Empagliflozin, Dapagliflozin, Ertugliflozin) provides protection against Cardiovascular events in patients with Type 2 Diabetes.Here, in our study we assessed the effects of SGLT2 inhibitors on cardiovascular outcomes via a comprehensive meta-analysis of data from the three randomized-placebo controlled trials. In addition to cardiovascular outcomes ,we also evaluated the adverse events associated with SGLT2 inhibitors[3,4].

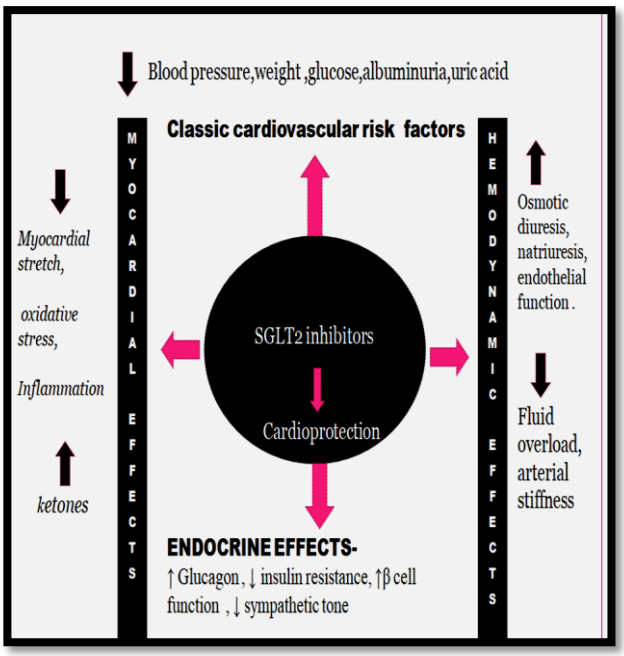

Fig.1. SGLT2 inhibitors and Cardiovascular benefits

A. *Study Objectives:*

- To identify and study the randomized controlled trials that evaluates the effects of individual SGLT2 inhibitors (Empagliflozin, Dapagliflozin and Ertugliflozin) on cardiovascular outcomes.
- To estimate the weight of the study and calculate the risk ratio for Major Adverse¬ Cardiovascular events, Hospitalization for Heart failure, Cardiovascular death and Mortality from any cause.
- To identify and estimate the severe adverse events associated with SGLT2 inhibitors.

II. METHODS

A. *Search Strategy*

The research question was constructed well in accordance to the PICO format.The Meta analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta – Analysis – PRISMA GUIDELINES[5].

A proper systematic literature search was conducted in the Pubmed database. The scientific search consists of effects of SGLT2 inhibitors and it's cardiovascular¬ outcome. The search strategy was restricted to only English language publications which were published from January 2015 - 2021.

B. *Study Selection Criteria*

The trials were selected based on the following study criteria: Inclusion Criteria : Randomised controlled trials that involved the study of three SGLT2 inhibitors¬ (Ertugliflozin, Dapagliflozin, Empagliflozin) on cardiovascular outcomes and adverse events. The randomized controlled trials with treatment intervention arm as¬ Empagliflozin, Dapagliflozin, Ertugliflozin and control arm as placebo. Trials that enrolled subjects with Type 2 diabetes along with the risk of¬ cardiovascular disease, irrespective of gender and age above 18 years. Studies that includes Case series, Case reports, Preclinical trials and Trials with follow up period less than 18 week were excluded.

C. *Data Extraction*

A total of 281 articles were identified in pubmed database. A sum of 114 duplicate records were removed and 167 records were screened. Only 75 articles were selected for their eligibility criteria and 66 Studies were excluded as they contained different outcomes of interest, other SGLT2 inhibitors As a result 3 Studies were included in our meta analysis.

The data were extracted manually that includes Generalized data and Treatment data. Study design of the trial, authors, year of publication, the number of study participants and their demographic characters like age, BMI, Range of HbA1c, duration of disease duration along wih the history of Cardiovascular or cerebrovascular risk were included in generalized data. Treatment data includes the treatment intervention and comparator used in the trial. The treatment follow up duration was also extracted.

To assess the risk of bias of individual Randomized controlled trials, we utilized the supplementary appendix for obtaining the following information such as methods involved in the trials like the Random sequence generation, patient allocation method, blinding techniques and the number of participants who withdrew from the trials. JADAD score was employed to assess the quality of each article. The articles with score more than 3 is considered to be of high quality.

D. ***Outcomes of interest***

The Meta analysis was performed to study the efficacy of SGLT 2 inhibitors on cardiovascular outcomes in Type 2 DM patients with the cardiovascular risk. Our meta analysis evaluated the cardiovascular efficacy outcomes of SGLT2 inhibitors and the following are the "Primary outcomes of interest

- 3 - point MACE – (Major Adverse Cardiovascular Events) that comprises of non fatal stroke, Non fatal myocardial infarction and a composite of cardiovascular death.
- Hospitalization for Heart failure
- Cardiovascular mortality
- All – cause mortality.

We examined the safety outcomes of SGLT 2 inhibitors in comparison with placebo. The secondary outcomes are adverse events associated with SGLT2 inhibitors such as

- Serious Adverse Events
- Hypoglycemia
- Acute kidney injury
- Fracture

E. ***Statistical Analysis***

Meta analysis was performed using the software – RevMan 5.4 version. Meta analysis was conducted for dichotomous data by using the fixed – effects model (Mantel – Haenszel model). The dichotomous variables were summarized as the number of events in correspondence to number of participants. The risk ratio (RR) with 95% confidence interval was estimated along with the weight of each study. The p value of the outcomes was determined by the z statistics. The heterogeneity across three studies was determined using chi – squared test. $I^2 < 50\%$ is associated with low heterogeneity, $I^2 > 50$ % is associated with high heterogeneity.

III. RESULTS

Three randomized – placebo controlled trials of 3 different SGLT 2 inhibitors **(**Empagliflozin, Dapagliflozin, Ertugliflozin) that met the inclusion /exclusion criteria were identified[6,7,8].

A. ***Study Characteristics***

A total of 32,426 participants were included in our Meta analysis. The mean age of all participants ranged from 63.1 – 64.4 years, the mean duration of diabetes in total participants was 11 years. The mean baseline HbA1c ranged from 8.07% to 8.3%. The average baseline systolic blood pressure ranged from 133.3 mmHg -135.5mmHg. The baseline eGFR (ml/min/1.73m^2) in the participants was scaled from 74.0 ml/min/1.73m^2 to 85.2 ml/min/1.73m^2. At screening of the total 32,426 participants 8611 (26.5 %) were reported with the history of coronary artery disease, 2194 (6.76 %) had the medical history of heart failure. In addition, 2414 participants were presented with the history of cerebrovascular disease. The median range of follow up duration of treatment was found to be 3.0 - 4.2 years.

B. ***Primary Cardiovascular Outcomes***

- Effects of SGLT2 inhibitors on the risk of 3 – point MACE (Major Adverse Cardiovascular Events)

All the 3 RCTs reported the effects of SGLT2 inhibitors on MACE outcomes as primary outcome. On the whole across the 3 randomized placebo controlled trials, 3311 patients were confronted with 3 - point MACE outcomes. Comparison of SGLT2 inhibitors with placebo,the SGLT2 inhibitors were associated with notable reduction in the risk for 3 point MACE – Major Adverse Cardiovascular Events (risk ratio =0.94; 95% CI;0.88-1.00). The Z statistics, p value is 0.06. The heterogeneity testing showed low grade heterogeneity with I^2 = 12%. The total weight of the study was found to be 74.8%.

- Effects of SGLT2 inhibitors on risk of Hospitalization for Heart failure:

SGLT2 inhibitors vs placebo, the results exhibited that SGLT 2 inhibitors markedly reduced the incidence of hospitalization for heart failure compared with placebo group (RR=0.71; 95% CI;0.63-0.81). The SGLT2 inhibitors reduced the risk of hospitalization for heart failure with zero evidence of heterogeneity I2 =0% . The total weight of the study was determined to be 25.2% .

C. ***Secondary Cardiovascular Outcomes***

- Effects of SGLT2 inhibitors on the risk of Cardiovascular death The SGLT 2 inhibitors on comparison with the placebo group substantially decreased the risk of cardiovascular mortality (RR =0.87; 95% CI,0.78 - 0.96).
- Effects of SGLT2 inhibitors on risk of All – cause mortality

SGLT 2 inhibitors vs placebo, the SGLT 2 inhibitors reduced the risk of all – cause mortality in patients with Type 2 DM and CV risk. SGLT 2 inhibitors decreased the risk of death from any causes compared with placebo (RR=0.87; 95% CI,0.82- 0.93).

D. ***Safety outcomes of SGLT2 inhibitors***

- **Serious Adverse Events**

Overall, 11687 patients in (intervention group + control group) were presented with serious adverse events.. On comparison of SGLT2 inhibitors vs placebo, outcomes exhibited that SGLT2 inhibitors did not increase the risk for serious adverse events (RR= 0.94; 95% CI, 0.91- 0.96) .

- **Hypoglycemia**

Among the 32,401 participants it was determined that 2540 patients had presented with hypoglycemia. On evaluation of adverse events occurring with SGLT2 inhibitors, the risk of hypoglycemia was found to be reduced (RR = 0.95; 95% CI, 0.89 - 1.03).

- **Acute Kidney Injury**

543 patients out of 32,401 patients had presented with acute kidney injury during the duration of treatment. SGLT2 inhibitors were associated with lower risk of developing

acute kidney injury the relative risk was estimated to be (RR = 0.73; 95% CI, 0.62 – 0.86).

- **Fracture**

It was estimated that overall 1,466 patients out of 32,401 had confronted with bone fracture and SGLT2 inhibitors were associated with moderate risk of developing fracture in comparison with placebo. There is a slight risk of developing fracture in patients with Type 2 DM when treated with SGLT2 inhibitors the relative risk (RR = 1.03; 95% CI, 0.93 – 1.14).

Table1. STUDY CHARACTERISTICS OF THE TRIALS

Characteristics	EMPA-REG TRIAL[6]	DECLARE TRIAL[7]	VERTIS –CV TRIAL[8]
Author/year of publication	Bernard Zinman 2015	S.D. wiviott 2018	C.P. Cannon 2020
Total no:participants (n)	7020	17160	8246
Treatment intervention-SGLT2 inhibitor	Empagliflozin 10mg or 25 mg once daily	Dapagliflozin 10mg once daily	Ertugliflozin 5mg or 15mg once daily
Control	Placebo	Placebo	Placebo
Age(yr)	63.1	63.9	64.4
HbA1c(%)	8.07	8.3	8.2
Body mass index (kg/m^2)	30.6	32.0	31.9
Duration of disease- Type 2 diabetes (yr)	11	11	11
Follow up median duration (yr)	3.1	4.2	3.0
Systolic blood pressure (mmHg)	133.5	134.9	133.3
Estimated Glomerular Filtration Rate (ml/min/1.73m^2)	74.0	85.2	75.9
History of coronary artery disease (no:)	2654	2829	3128
History of cerebrovascular disease (no:)	819	650	945
History of heart failure (no:)	353	862	979
JADAD score	5	5	5

MEAN ± SD CHARACTERISTICS OF TRIAL PARTICIPANTS WERE CALCULATED

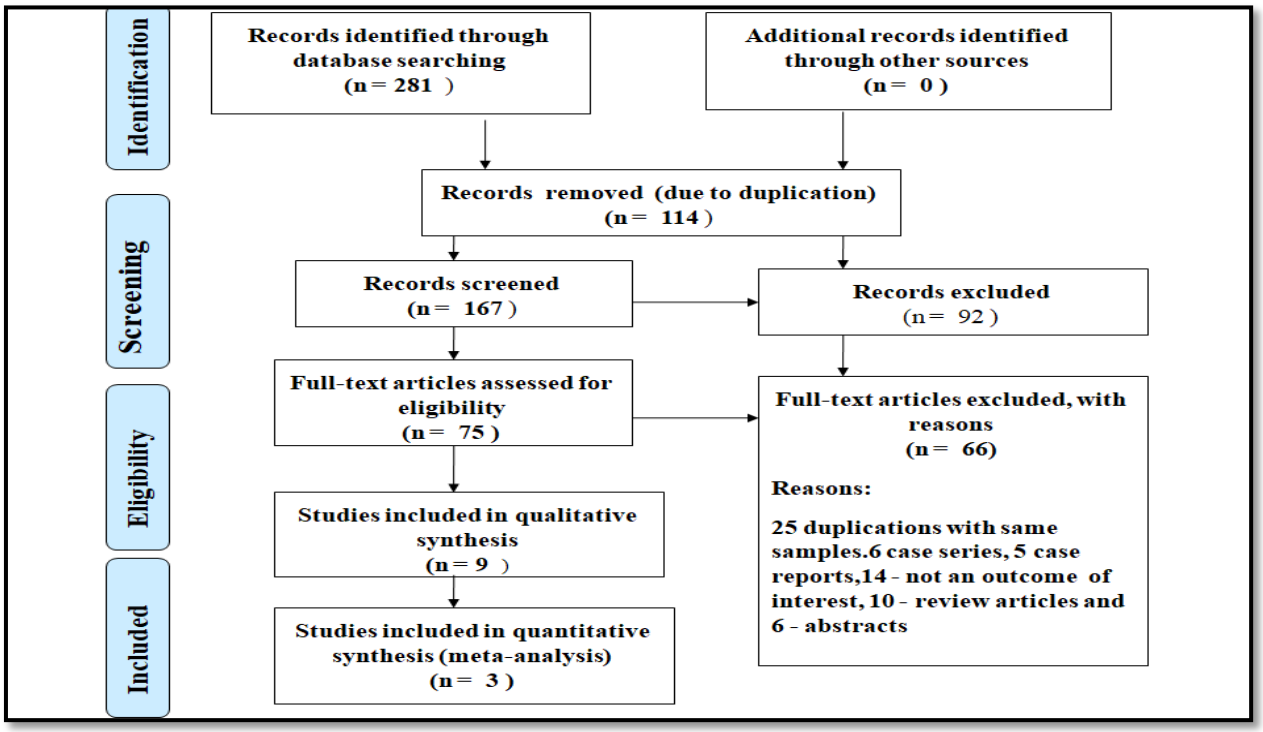

Fig.2.PRISMA FLOW DIAGRAM

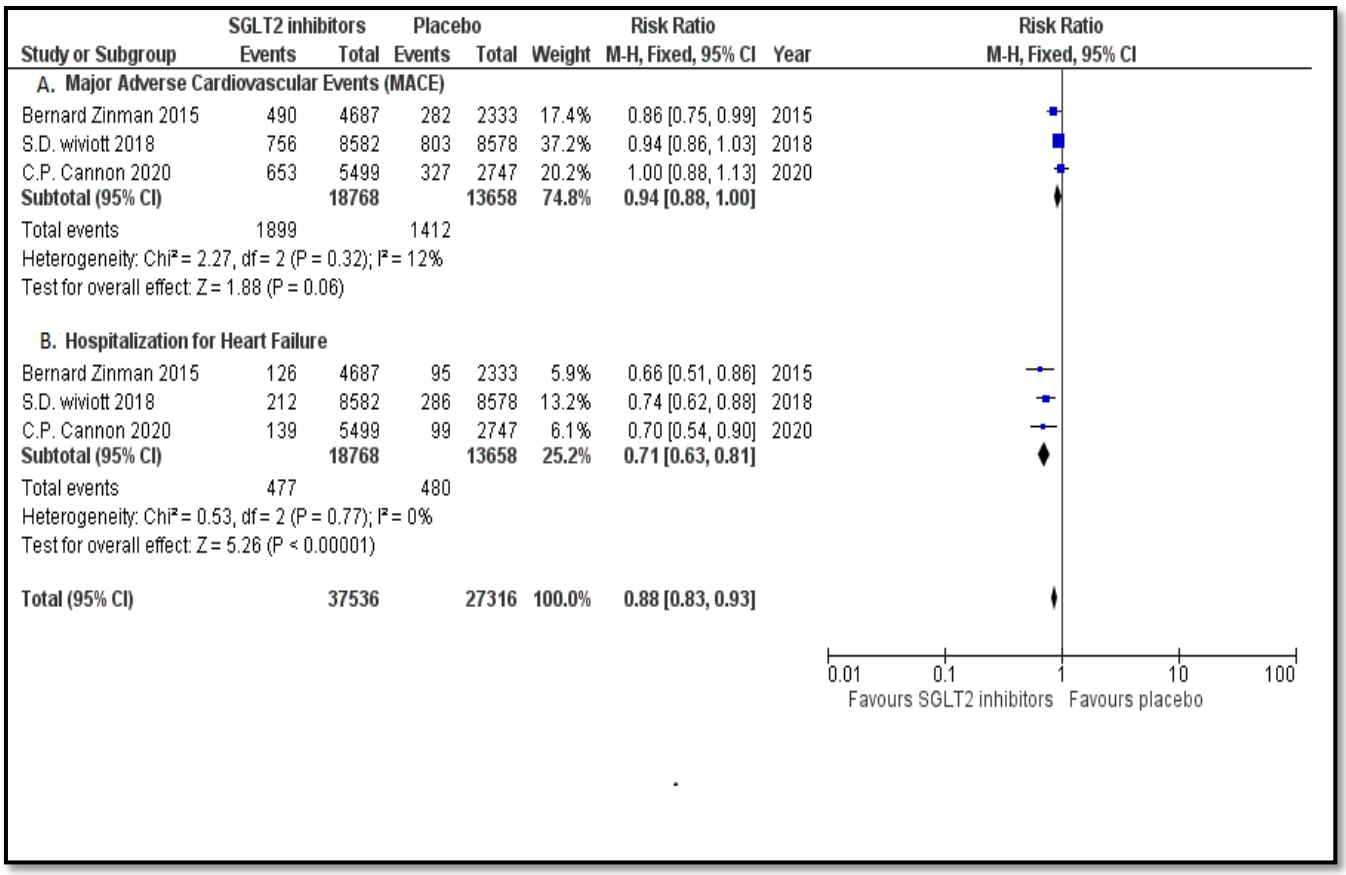

Fig.3 Forest plot for meta-analysis of the effects of SGLT2 inhibitors on primary cardiovascular outcomes

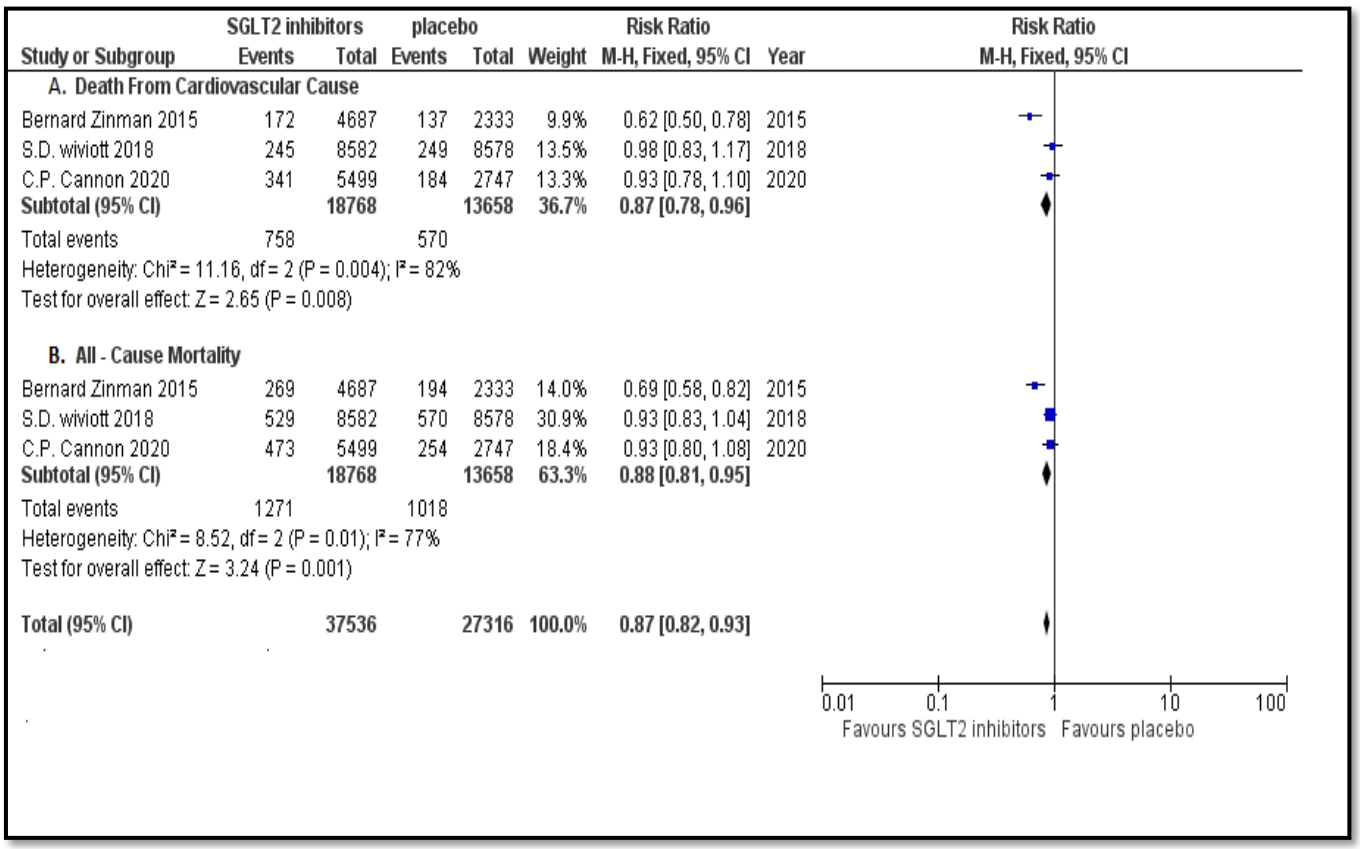

Fig.4.Forest plot for meta-analysis of the effects of SGLT2 inhibitors on secondary cardiovascular outcomes

ISSN No:-2456-2165

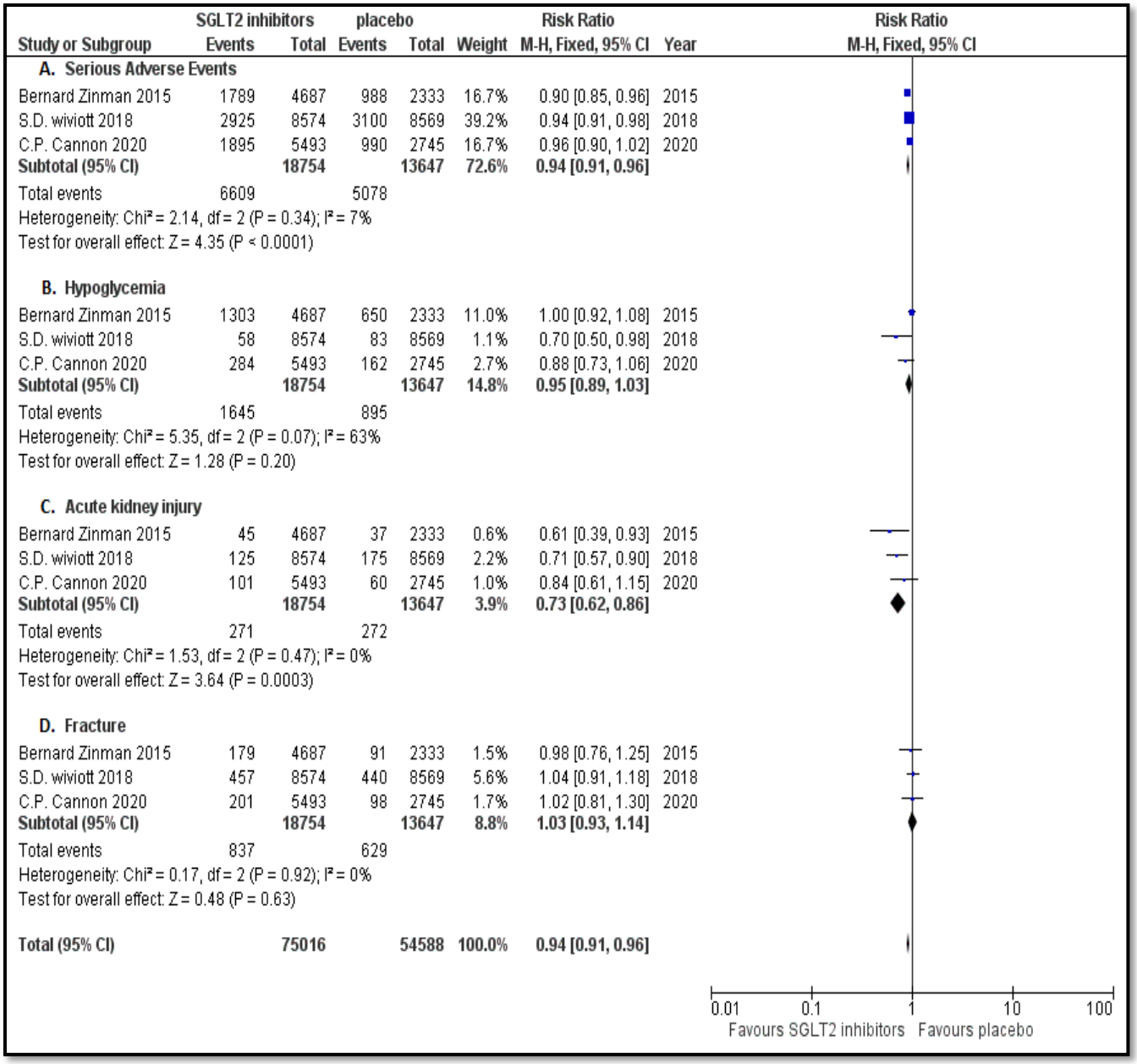

Fig.5.Forest plot for meta-analysis of the safety outcomes of SGLT2 inhibitors

IV. DISCUSSION

Our Meta-analysis includes the data from clinical trial (EMPA - REG TRIAL, DECLARE TIMI TRIAL, VERTIS CV TRIAL outcomes involving the SGLT 2 inhibitors - Empagliflozin, Dapagliflozin, Ertugiflozin.

It was analyzed that SGLT 2 inhibitors were associated with decreased risk of 3 point MACE – Major Adverse Cardiovascular Events (Non fatal Myocardial Infarction, Non fatal stroke, Composite of CV death), HHF- Hospitalization for heart failure, Cardiovascular Mortality and All – cause mortality. From the results of our Meta analysis, we identified that the SGLT 2 inhibitors can potentially protect the Type 2 DM patients against the cardiovascular events like hospitalization for Heart failure, 3 point MACE – (Myocardial infarction, Non fatal Stroke and Cardiovascular death).

The safety outcomes of SGLT 2 inhibitors were also established in our Meta analysis. SGLT 2 inhibitors were not associated with increased risk of serious adverse events. The secondary safety outcomes included Hypoglycemia, Acute kidney injury and Fracture. It was found that the incidence of hypoglycemic risk was low. The SGLT 2 inhibitors did not increase the risk of Acute kidney injury. A minor evidence of bone fracture risk was identified. Our Meta analysis investigated the effects of SGLT 2 inhibitors (Empagliflozin, Dapagliflozin and Ertugliflozin) on cardiovascular outcomes in Type 2 DM patients and our study has produced reliable results stating that the patients who were treated with SGLT 2 inhibitors had experienced favourable cardiovascular outcome.

Few limitations are also recognized in our study. There is no information regarding the other oral hypoglycemic medications with concomitant administration of SGLT2 inhibitors in all of the 3 clinical trials. The literature search strategy was done only using single database for identifying the eligible studies.The results are analyzed for study level data only ,the individual patient data was not provided for the included randomized controlled trials.

V. CONCLUSION

In conclusion, our study is an attempt to scrutinize more on clinical trials related to SGLT2 inhibitors and their cardioprotective action. On performing a further profound research these study results would state the potential of SGLT2 inhibitors in reducing the cardiovascular events. Our study provides a evidence that SGLT2 inhibitors is associated with reducing the risk of cardiovascular death and hospitalization for heart failure, thus it provides a notable cardioprotective effects. The results of our study suggests that Empagliflozin is likely to be more effective in reducing the risk of cardiovascular death, major adverse cardiovascular events and hospitalization for heart failure.

Also, Dapagliflozin and Ertugliflozin are potent in reducing the risk of hospitalization for heart failure. Hence, our assessment is suggestive to incorporate this class of Oral hypoglycemic agents i.e SGLT2 inhibitors in type 2 diabetes patients with the risk of cardiovascular complications.

REFERENCES

[1]. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2019 Nov 1;157:107843.

[2]. Mohan , H. The Endocrine System. In: Damjanov , I (ed.) Textbook of Pathology. New Delhi,India: Jaypee Brothers,Medical Publishers Pvt Limited,; 2014.7th ed:p:808-818.

[3]. Verma S. Potential Mechanisms of Sodium-Glucose Co-Transporter 2Inhibitor-Related cardiovascular Benefits. The American Journal of Medicine. 2019;132(10):S39-S48.

[4]. Li WJ, Chen XQ, Xu LL, Li YQ, Luo BH. SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials. Cardiovascular diabetology. 2020 Dec;19(1):1-4.

[5]. PRISMA. Prisma-statement.org. 2021. Available from: http://prisma-statement.org/PRISMAStatement/FlowDiagram

[6]. Zinman B, Wanner C, Lachin J, Fitchett D, Bluhmki E, Hantel S et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine. 2015;373(22):2117-2128.

[7]. Wiviott S, Raz I, Bonaca M, Mosenzon O, Kato E, Cahn A et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2019;380(4):347-357.

[8]. Cannon C, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. New England Journal of Medicine. 2020;383(15):1425-1435.