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The Effects of SGLT2 Inhibitors on Cardiovascular Outcome and Renal Disease in Type 2 Diabetic Patients Established Cardiovascular Disease and Moderate Chronic Kidney Disease: Systematic Review and Meta Analysis

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ABSTRACT

Background: Diabetes patients are at high risk for mortality due to cardiorenal cause. Although multiple pharmacological drugs are available but SGLT2 (sodium glucose transporter 2) inhibitors efficacy in reducing incidence of cardiovascular and renal outcome in diabetic patients with both CKD (chronic kidney disease) and established cardiovascular disease are not clearly demonstrated. This systematic review with meta-analysis will address this with following studies.

Method: Studies for this meta-analysis was been searched with PubMed, Cochrane from 2010 till 2023. Studies were screened in accordance with PRISMA updated version. Statistical analysis was done in JAMOVI software. Risk ratio with 95%CI with fixed model effect was done to find the effects of SGLT2inhibitors across various studies in reducing the incidence of cardiorenal outcome.

Results: In total, 8 studies were been included for this meta-analysis. Overall, 49,034 patients were been included; 27,069 participated in treatment group and 21,965 participated in control group. Across 8 studies, mean age is 63, mean follow-up was 2.6 years. overall, there was significant reduction in CV outcome with fixed effect model -0.1482, p = 0.0008 (95% CI: -0.2345 to -0.0618). In addition, SGLT2 inhibitors has reduced risk of all cause death -0.1203 (95% CI: -0.1869 to -0.0536), hospitalization for heart failure -0.3851 (95% CI: -0.4623 to -0.3078) and composite renal outcome -0.4170 (95% CI: -0.5347 to -0.2994) with minimal risk of heterogeneity.

Conclusion: The result of this systematic review suggests that SGLT2 inhibitors have significant efficacy in reducing the incident of cardiovascular death and composite renal outcome which proves the protective role of drug in both established cardiovascular disease and moderate CKD patients in type 2 diabetes.

Keyword: Estimated glomerular filtration rate; Albuminuria; Cardiorenal outcome; Heart failure; Composite renal outcome

BACKGROUND

Type 2 diabetes is one of the common metabolic disorder prevalent worldwide. It is characterized by elevated blood glucose level, impaired insulin secretion and high insulin resistance, which is diagnosed as per WHO by HbA1C ≥6.5% or fasting blood glucose ≥7 mmol/ liter [1]. As per international diabetes federation 12.8%(4.8million) of diabetic patients belong to age group 20-79 years old, which could increase to 15.7% by 2045(37).

Diabetes is a serious chronic disease associated with substantial risk for multiple microvascular and macrovascular complications. Particularly, macrovascular complication like Myocardial infarction, stroke, end stage kidney disease .4.2 million death are happening in age group of 20 to 79 years old, which is attributed to.11.3% of death worldwide are due to diabetes particularly below 60 years old [2]. More premature death happening in diabetes patient, which are due to diabetic complication rather than diabetes alone[3]. Elevated blood glucose is associated with 15% of all cause death due to cardiovascular disease, renal disease and diabetes [4]. Therefore, essential part in diabetes is to prevent such premature death in diabetes by early detection of type 2 Diabetes or diabetic complications.

The presence of diabetes and cardiovascular disease has shown to increase the risk of mortality [5]. The characteristics metabolic impairment in diabetic patients are hyperglycemia , excessive free fatty acid, insulin resistance ,which end up in reduced nitric Oxide production and activation of renin- angiotensin system ,leads to endothelial dysfunction [6] .This contributes to hypertension or arterial stiffness, which partially explain the risk of vascular events in diabetic patients[7] .The risk of heart failure(HF) in diabetic patients are multifactorial ,few studies shown that heart failure are independent of coronary artery disease and studies are lacking in appropriate pharmacological intervention to tackle cardiovascular outcome in diabetic patients[8,9]. Hence, drugs determined for diabetic treatment should not only focus on diabetes but also to prevent cardiac mortality in diabetic patients [10,11]. However, there are also few studies concerned that intensive glucose lowering agents or specific group of anti-diabetic agents are associated with adverse cardiac outcome [12], which emphasize the importance of evaluating the cardiovascular safety of anti-diabetic medication [13].

SGLT2 inhibitors are becoming popular as they have shown some benefit in diabetic patients with cardiovascular disease risk. SGLT2 inhibitors are dapagliflozin, empagliflozin, ertugliflozin, Sota gliflozin, canagliflozin. These drugs act by reducing resorption of glucose in kidney proximal tubules, which leads to excessive excretion of glucose in urine [5]. This mechanism of action is independent of insulin .SGLT2 inhibitors has shown significant reduction in BP and weight, which is considered to be vital action of SGLT2 inhibitors in reducing the vascular events in diabetes [13,14]. In addition, reduction in intraglomerular pressure, reducing albuminuria are proving the protective mechanism against cardiorenal outcome [15]. But still studies are lacking to prove protective effect of SGLT2 inhibitors on diabetic patients with both established cardiovascular disease and moderate chronic kidney disease. In addition, SGLT2 inhibitors were reluctant to use among type 2 diabetic patients with chronic kidney disease patients and older patients due to their adverse events on renal system. But , in recent time there are multiple studies involving chronic kidney disease with type 2 diabetes are treated with SGLT2 inhibitors and long-term follow-up done, which has shown insignificant progression of CKD and similar beneficial effect as seen in patients without CKD on composite renal outcome like renal death, new onset of end stage kidney disease (ESKD) ,≥40% of eGFR reduction [16-18]. Few studies

has shown similar effects on cardiovascular outcome in both younger and older patients treated with SGLT2 inhibitors for reducing cardiovascular outcome.

As the effect of SGLT2 inhibitors are on renal proximal tubule, they are directly dependent on glomerular filtration rate. Therefore, their efficacy was assumed to be reduced with reducing eGFR rate. Recently systematic review with meta-analysis [19] was done using various SGLT2inhibitors on cardiorenal outcome irrespective of diabetes. Totally 13trial were selected for analysis, 82.7% participants were diabetic and 17.3% were non-diabetic. Results showed SGLT2 inhibitors reduced progression of renal disease by 37%, reduced risk of acute kidney injury by 23%, reduced risk if cardiovascular death or hospitalization for heart failure by 23% but risk of non-cardiac death rate was not significantly reduced. All the outcome were similar in diabetic as well as non-diabetic patients. Results were produced irrespective of baseline eGFR. This analysis has included participants with chronic kidney disease. Therefore, they have proved better cardiorenal risk reduction even in presence of chronic kidney disease patients irrespective of diabetes. The current meta-analysis will evaluate similar effect in presence of diabetes and moderate chronic kidney disease.

Among SGLT2 inhibitors, empagliflozin was the first drug approved to use in patients with history of cardiovascular disease. A study by Anker et al., 2021 [20] has used empagliflozin in patients with NYHA class 2-4 stage of heart failure with an ejection fraction >40% has shown reduction in rate of incidence of cardiac death and hospitalization for heart failure in treatment group.

To our best of knowledge, there were no systematic review with meta-analysis were conducted to evaluate the efficacy of SGLT2 inhibitors in reducing cardiorenal outcome like cardiac death, all cause death, hospitalize for heart failure or composite renal outcome among type 2 diabetic patients with both risk factors like established cardiovascular disease and moderate chronic kidney disease. Therefore, this systematic review with meta-analysis will address the risk reduction caused by this drug on cardiorenal outcome in type 2 diabetes patients with both established cardiovascular disease and moderate CKD patients. Through such meta-analysis results, we could suggest recommendations on individualizing the treatment plan based on patients profile in type 2 diabetic patients with risk factors.

METHODOLOGY

The current systematic review with meta-analysis has followed PRISMA guideline [21]

Data source

Two electronic database (Cochrane, PubMed) was used to search clinical trials published in English from the year 2010 till July 2023. Data search done on 28/07/2023 with advanced keyword search (((((((cardiorenal outcome)) AND (SGLT2inhibitor)) OR (empagliflozin)) OR (dapagliflozin)) OR (ertugliflozin)) OR (canagliflozin)) OR (Sota gliflozin) **AND (type 2diabetes mellitus) OR (non-insulin dependent diabetes) OR (Diabetes mellitus)** in different combination PubMed. In Cochrane **diabetes mellitus" in All Text AND SGLT2inhibiotrs in Title Abstract Keyword AND cardiorenal outcome in Title Abstract Keyword – (Word variations have been searched)**. Filters used which include only Randomized clinical trial conducted between 2010 to July 2023, with full free text, published in English, only studies conducted in humans.

Study selection

Inclusion criteria

1) Only randomized controlled trials are included
2) Studies involving human subjects
3) Studies examining SGLT2inhibitors with placebo are involved
4) ≥18years with T2DM defined as per WHO characterized by HbA1c ≥6.5% or fasting blood glucose ≥7 mmol/liter [22].
5) Study Patient should has established cardiovascular disease or high risk for cardiac outcome (1) and should have chronic kidney disease.
6) Study duration should be more than 6month
7) Studies outcome should explore on cardiorenal outcome.

Exclusion criteria

1) Exclude studies if language other than English
2) Exclude case studies, case series
3) Patients with type 1 diabetes, Gestational diabetes, severe chronic kidney disease <30ml /min/1.73m² are excluded.
4) Sub analysis of involved trials and duplicate studies are excluded
5) Studies comparing other drugs except for placebo will be excluded.

Quality assessment

Each study's methodology was carefully assessed using JADAD score [23]. It is a 5-point scale for measuring quality of randomized trials .1) randomization is mentioned 2) method of randomization is appropriate 3) blinding mentioned 4) method of blinding is appropriate 5) outcome of all participant including number of dropout and reason for dropouts are mentioned. Score of 3or more indicate high quality studies [4,11], which denote that we are very confident that the true effect is close to the estimate effect.

Data extraction

From all the selected studies, detailed information on characteristics, study methodology, intervention, control group and follow-up period were been collected. In patient characteristics, mean age, total number of participants in control and intervention group, follow-up period, duration of diabetes disease and mean HbA1C levels were been noted across studies.

In terms of cardiorenal risk factors like [25], number of participants with established cardiovascular disease, heart failure, NTproBNP level, angina, hypertension, chronic kidney disease status, albuminuria, estimated glomerular filtration rate (eGFR) are been compared across studies.

Most of the studies had explored outcome like cardiac death, all cause death, hospitalization of heart failure, composite renal outcome, hence these 4 outcomes [1,31,25-30] were used in this analysis for better comparison and to find appropriate results pertaining to it. Other outcome like non-fatal myocardial infarction, non-fatal

stroke, silent MI, different albuminuria level was not broadly studied in most of studies therefore those outcomes were been rejected from analysis. Moreover, they are not associated with more mortality [10,12] when compared to 4 principal outcomes selected for this Meta analysis. Composite renal outcome is defined as sustained reduction of >40% eGFR calculated by means of chronic kidney disease epidemiology collaboration equation to <60ml /min / 1.73m² of body surface area, new end stage renal disease, or death from renal or cardiovascular causes [7].

Data analysis

Each study will be screened for above mentioned inclusion, exclusion criteria, outcome. Meta analysis is conducted using JAMOVI software. Initially heterogeneity is assessed by Q statistic and I^2 test (18). I^2 test range from 0-100%; where <25% is minimal risk for heterogeneity, 25-75% with moderate amount of risk for heterogeneity and >75% are associated with high risk for heterogeneity. If heterogeneity is found to be high across studies, then sub group analysis will be performed to detect true effect value. Separate meta-analysis for each outcome (Cardiovascular death, all cause death, hospitalization for heart failure, composite renal outcome) were been done using Fixed effect method if most of results were consistent or random effect model if heterogeneity is high and forest plot with 95%CI are reported. P<0.05 are considered significant difference beyond chance in heterogeneity test. Publication bias was reported using Egger's regression test [6] and funnel plot presented.

RESULTS

Study selection

Systematic search strategy was used in accordance with PRISMA updated version 2021[2]. Two databases were used PubMed and Cochrane. Totally 1660 studies were been retrieved from PubMed (495), Cochrane (1165). EndNote was used to do screening for duplicate studies, 128 duplicate studies were been removed, 1119 studies are been excluded based upon text and abstract, 126 studies excluded as they do not have access to free full text. Remaining 287 studies were been evaluated, based upon exclusion criteria 221 studies removed as they involved severe CKD, type1diabetes and other exclusion criteria. 5 studies removed as the study duration was <6month, 38 studies removed as they have used different comparator (GLP1 agonist, pioglitazones, insulin, sulfonylureas), 15studies provided irrelevant outcome. Therefore, 8 studies matching inclusion criteria were been finalized and included in this meta-analysis. (Screening procedure detailed in figure 1)

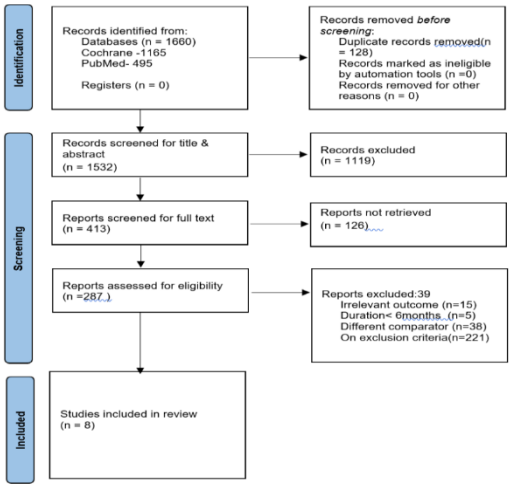

Figure 1: PRISMA FLOW CHART

Table 1: Characteristics of studies included in meta-analysis

AUTHOR & DATE	STUDY DESIGN	NUMBER OF SUBJECT IN TREATMENT /CONTROL GROUP	MEAN AGE IN TREATMENT /CONTROL GROUP	TREATMENT DOSE	CONTROL GROUP	FOLLOW UP	PATIENT CHARACTERISTICS	JADAD score	Quality
Zinman et al., 2015 (1)	RCT	4687/ 2333	63.1/63.2	Empagliflozin 10mg or 25mg once daily	Placebo	3.1 year	T2DM CV risk CKD	3	High
Wiviott et al.,2018(2)	RCT	8582/ 8578	63.9/64.0	Dapagliflozin 10mg once daily	Placebo	4.2 years	T2DM CV risk	4	high
Perkovic et al., 2019(3)	RCT	2202/ 2199	62.9/63.2	Canagliflozin 100mg once daily	Placebo	2.62 years	T2DM CV risk CKD	3	high
Cannon et al., 2020(4)	RCT	5499/ 2747	64.4/64.4	Ertugliflozin 5mg or 15mg once daily	Placebo	3.5years	T2DM CV risk CKD	5	High
Bhatt et al., 2021 .1(5)	RCT	5292/ 5292	69/69	Sotagliflozin 200mg once daily	Placebo	30month	T2DM CV risk CKD	4	High
Bhatt et al.,2021 .2(6)	RCT	608/6 14	69/70	Sotagliflozin 200mg once daily	Placebo	18month	T2DM CV risk CKD	4	high

Adel et al., 2022(7)	RCT	45/48	55/57	Empagliflozin 10mg once daily	Placebo	6month	T2DM CV risk CKD	4	high
Wada et al.,2022(8)	RCT	154/154	62.5/62.4	Canagliflozin 100mg once daily	Placebo	30month	T2DM CV risk CKD	3	high

RCT -randomized control trial, T2DM – type 2 diabetes mellitus, eGFR – estimated glomerular filtration rate, CV risk – cardiovascular risk, HF – heart failure CKD- chronic kidney disease

Table 2: Established cardiorenal risk factors in included studies

AUTHOR AND DATE	**CARDIOVSCULAR RISK Number of affected patients in T/ C**	**RENAL DISEASE (CKD/ eGFR) Number if affected patients in T/ C**	**DIABETES (mean duration or Mean HbA1C) T/ C**	**OUTCOME MEASURED**
Zinman et al.,2015	Coronary artery disease – 2732/1340	eGFR<60ml-1212/607	HbA1C <8.5%-3212/1607	CV death, HHF
Wiviott et al.,2018	Established CV disease- 3474/3500 HF- 852/872	-	HbA1C-8.3/8.3 Duration of T2DM-11/10	CV death, All cause death, HHF, composite renal outcome
Perkovic et al.,2019	Established CV disease – 1113/1107 HF-329/323	eGFR-56/56	Duration of T2DM-15/16	CV death, All cause death, HHF, composite renal outcome
Cannon et al., 2020	Coronary artery disease- 4144/2112 HF- 1286/672 MI- 2625/1329	eGFR- 76.1/75.7	HbA1c – 8.2/8.2 Duration of T2DM-12.9/13.1	CV death, All cause death, HHF, composite renal outcome
Bhatt et al.,2021.1	CVS risk factor at least one major – 4682/4699 History of HF – 1640/1643	eGFR- 44/44	HbA1C- 8.3/8.3	CV death, All cause death, HHF, composite renal outcome
Bhatt et al.,2021.2	Mean EF- 35/35% Mean NT ProBNP-1816/1741	eGFR – 49/50	HbA1C – 7.1/7.2	CV death, All cause death, HHF
Adel et al.,2022	STEMI – 27/23 NSTEMI- 2/4 Unstable angina – 16/21 HTN- 26/32	CKD – 4/3	Duration of T2DM – 6/6	CV death
Wada et al.,2022	HTN -154/154	eGFR – 56.3/55.2	HbA1C- 7.75/7.77 Duration of T2DM – 15.43/16.49	All cause death, Composite renal outcome

T2DM – type 2 diabetes mellitus, eGFR – estimated glomerular filtration rate, CV risk – cardiovascular risk, HF – heart failure CKD- Chronic kidney disease, HHF – hospitalization for heart failure, STEMI – ST elevate Myocardial infarction, MI-myocardial infarction, HTN – hypertension, EF – ejection fraction, T- treatment group, C- control group

Characteristics of studies

Totally eight placebo controlled randomized studies of five SGLT2 inhibitors(Dapagliflozin[8] , canagliflozin [27,17], empagliflozin [1,7],ertugliflozin[4], sotagliflozin [5,6])in T2DM patients with high risk for cardiovascular disease and renal disease were been identified and cohort characteristics illustrated in Table 1&2. Overall, from eight studies 49,034 patients were been included; 27,069 participated in treatment group and 21,965 participated in control group. Across 8 studies, mean age is 63, mean follow-up was 2.6 years. Six studies have mentioned the mean HbA1c, average HbA1c level range from 8%-8.3% and five studies show T2DM duration with average range around 11years. All the studies had placebo as comparator.

All the 8 studies show established or high risk for cardiovascular disease and renal disease .7 studies shows majority of participants with established cardiovascular disease [26-32], high risk for cardiovascular disease [5,8]. Five studies have shown established chronic kidney disease [5-8,3], other studies show eGFR <60ml /min / 1.73m² of body surface area which indicate mild CKD.

Outcome of four studies [27-31] have shown CV death, all cause death, HHF, composite renal outcome, only CV death reported in [7]. All the 8 studies have shown CV death.

Table 1: Characteristics of studies included in meta-analysis

Cardiovascular death (CV death)

A total of eight studies were included in this meta-analysis. The observed log risk ratios ranged from -0.6286 to 1.0986, with the majority of estimates being negative (88%). The estimated average log risk ratio based on the fixed-effects model was -0.1482 (95% CI: -0.2345 to -0.0618). Therefore, the average outcome differed significantly from zero (z = -3.3640, p = 0.0008) Figure 2A. The Q-test for heterogeneity was not significant, but some heterogeneity may still be present in the true outcomes (Q =13.3589, p = 0.0638, I^2 = 47.6005%). An examination of the studentized residuals revealed that one study (zinman et al., 2015) had a value larger than ± 2.7344 and may be a potential outlier in the context of this mode. The 95%CI of wiviott et al.,2018; cannon et al.,2020; Bhatt et al.,2021.2; Adel et al.,2022; Wada et al., 2022 cross the line of no effect which reveals that the results of those individual studies may not be significant. But, 95% CI of other studies does not cross null effect, those results are significant. Although majority of studies had crossed null effect but pooled effect of risk ratio shows significant reduction -0.1482, p = 0.0008 (95% CI: -0.2345 to -0.0618) in treatment group than in placebo group.

All cause death

Total of seven studies are included in this analysis. The observed log risk ratios ranged from -0.3708 to 0.0000, with the majority of estimates being negative (71%). The estimated average log risk ratio based on the fixed-effects model was = -0.1203 (95% CI: -0.1869 to -0.0536). Therefore, the average outcome differed significantly from zero (z = -3.5370, p = 0.0004) which shows that SGLT2 inhibitors have significantly reduced incidence of all cause death compared to placebo (Figure 2B). The Q-test for heterogeneity was not significant, but some heterogeneity may still be present in the true outcomes (Q = 10.9061, p = 0.0913, I^2 = 44.9849%). An examination of the studentized residuals revealed that one study (zinman et al., 2015) had a value larger than ± 2.6901 and may be a potential outlier in the context of this model. 95%CI of all studies are crossing the line of

null effects, which denote non-significant results of individual studies. But overall pooled effect shows significant reduction of incidence of all cause death in SGLT2 inhibitor than in placebo group.

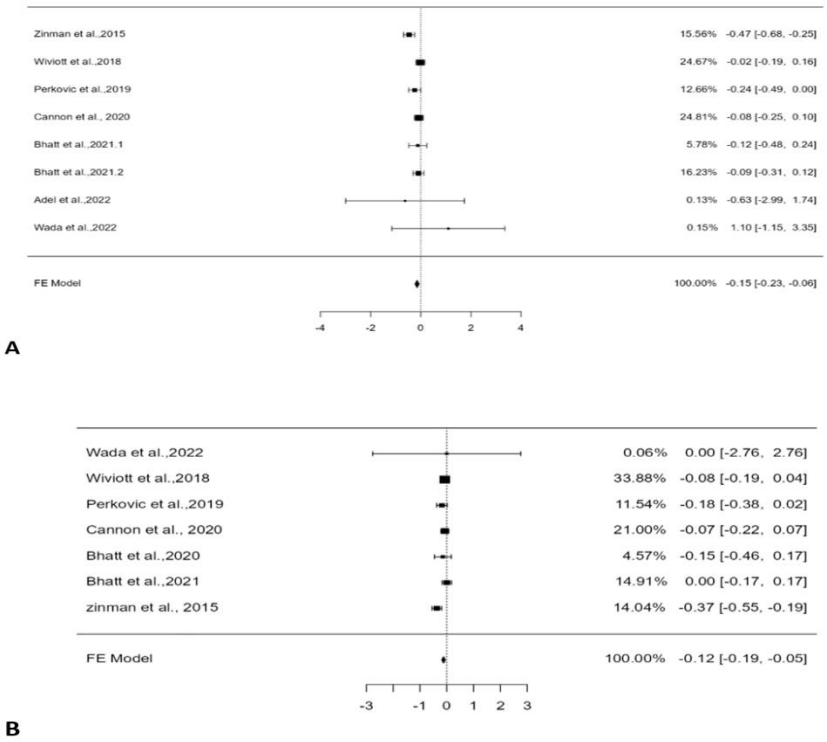

FIGURE 2A: *FOREST PLOT COMPARING EFFECT OF SGLT2 INHIBITORS WITH PLACEBO IN INCIDENCE OF CARDIOVASCULAR DEATH, BASED UPON FIXED EFFECT MODEL WITH 95% CONFIDENCE INTERVAL. B IS FOREST PLOT COMPARING THE EFFECT OF SGLT2INHIBITORS AND PLACEBO ON INCIDENCE OF ALL CAUSE DEATH, BASED UPON FIXED EFFECT MODEL EFFECT WITH 95% CONFIDENCE INTERVAL.*

Hospitalization for heart failure

A total of seven studies were included in this analysis. The observed log risk ratios were ranging from -1.0986 to -0.2999, with the majority of estimates being negative (100%). The estimated average log risk ratio based on the fixed-effects model was -0.3851 (95% CI: -0.4623 to -0.3078). Therefore, the average outcome differed significantly from zero ($z = -9.7729$, $p < 0.0001$). According to the Q-test, there was no significant amount of heterogeneity across studies in the true outcomes ($Q = 1.9195$, $p = 0.9270$, $I^2 = 0.0000\%$). Overall, SGLT2 inhibitors significantly reduced the hospitalization for heart failure in comparison to placebo with no heterogeneity across studies (Figure 3A) .95% CI of all studies except wads et al., 2022 does not cross the line of null effect., this denote that he results of each individual study results shows significant reduction of incidence of hospitalization for heart failure in treatment group than placebo group. Therefore, this overall result proves to have supportive evidence for risk reduction 0.3851 (95% CI: -0.4623 to -0.3078) in patient treated with SGLT2 inhibitors.

Composite renal outcome

A total of five studies were used in analysis of composite renal outcome. The observed log risk ratios ranged from -0.9163 to -0.2114, with the majority of estimates being negative (100%). The estimated average log risk ratio based on the fixed- effects model was -0.4170 (95% CI: -0.5347 to -0.2994). Therefore, the average outcome differed significantly from zero (z = -6.9486, p < 0.0001, SGLT2 inhibitors shows significant reduction in incidence of composite renal outcome (Figure 3b) with moderate amount of heterogeneity across studies in the true outcomes (Q= 7.6941, p = 0.1034, I^2 = 48.0124%). Most of the studies 95% CI are toward left of null effect, in favor of SGLT2 inhibitors. Hence, pooled effect shows significant risk reduction of composite renal outcome in patient treated with SGLT2 inhibitors than placebo. 95% CI of higher weightage studies like wiviolett et al., 2018 ; perkovic et al., 2019 are towards left of line of null effect , which contributed mainly to pooled effect in favor of SGLT2 inhibitors.

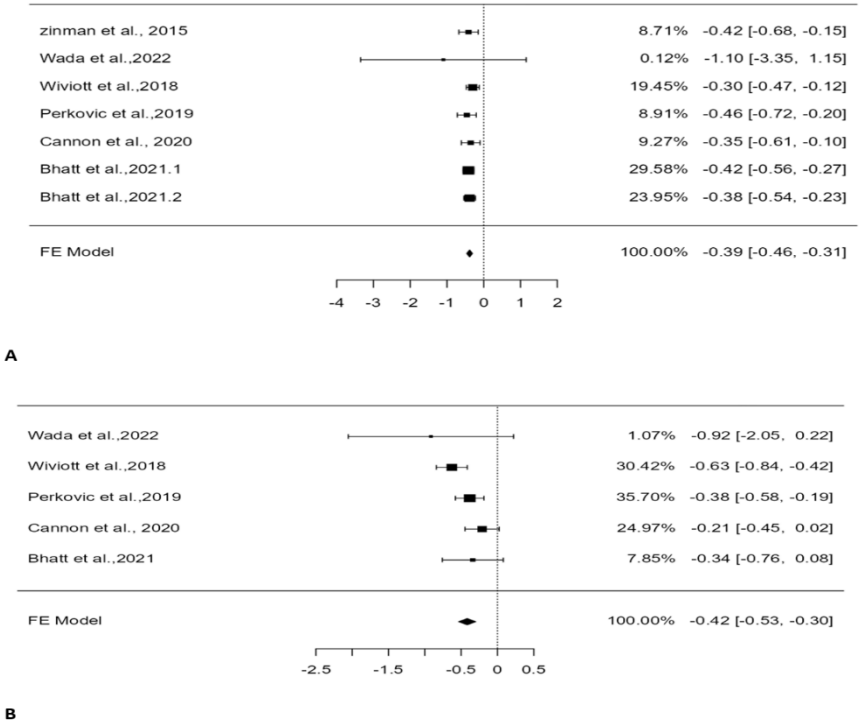

FIGURE 3A: *FOREST PLOT COMPARING EFFECT OF SGLT2 INHIBITORS WITH PLACEBO ON HOSPITALIZATION FOR HEART FAILURE, BASED UPON FIXED EFFECT MODEL RESULTS WITH 95%CONFIDENCE INTERVAL. B) FOREST PLOT COMPARING EFFECT OF SGLT2 INHIBITORS WITH PLACEBO ON INCIDENCE OF COMPOSITE RENAL OUTCOME, BASED UPON FIXED EFFECT MODEL RESULTS WITH 95% CONFIDENCE INTERVAL.*

Quality assessment and potential bias

Publication bias were assessed by egger's regression test (Figure 4) which shows no significant publication bias for CV death, all cause death, hospitalization for heart failure, composite renal outcome (P= 0.580, P= 0.451, P= 0.547 and P= 0.676).

JADAD scoring was used to assess risk of bias in each study. Table 1 details on Jadad scoring , overall each studies scored 3-5 which was considered to be high quality of studies with minimal bias across studies [9]. All the studies have mentioned about previous history of cardiovascular events or high risk for CV disease with various criteria like based on history of coronary artery disease [1-4] or number of major risk factor for CVS disease [5,8], or number of heart failure or MI [2-4,6]. But only 5 studies detailed on CKD [3,5-8] whereas other studies poorly detailed on CKD. All the studies have mentioned about randomization and appropriate randomization method like computer randomization technique or random sequence like 1:1 or 1:1:1. Blinding was done by 5 studies but only 3 studies have mentioned appropriate method of blinding .3 studies have used double blinding technique, which could help to evaluate the true effect of SGLT2 inhibitors on cardiorenal outcome among type 2 diabetic patients with both cardiovascular disease and moderate CKD. Other 2 studies have mentioned blinding, but further data on blinding were been. 6 studies have mentioned about outcome of all participants including dropouts.

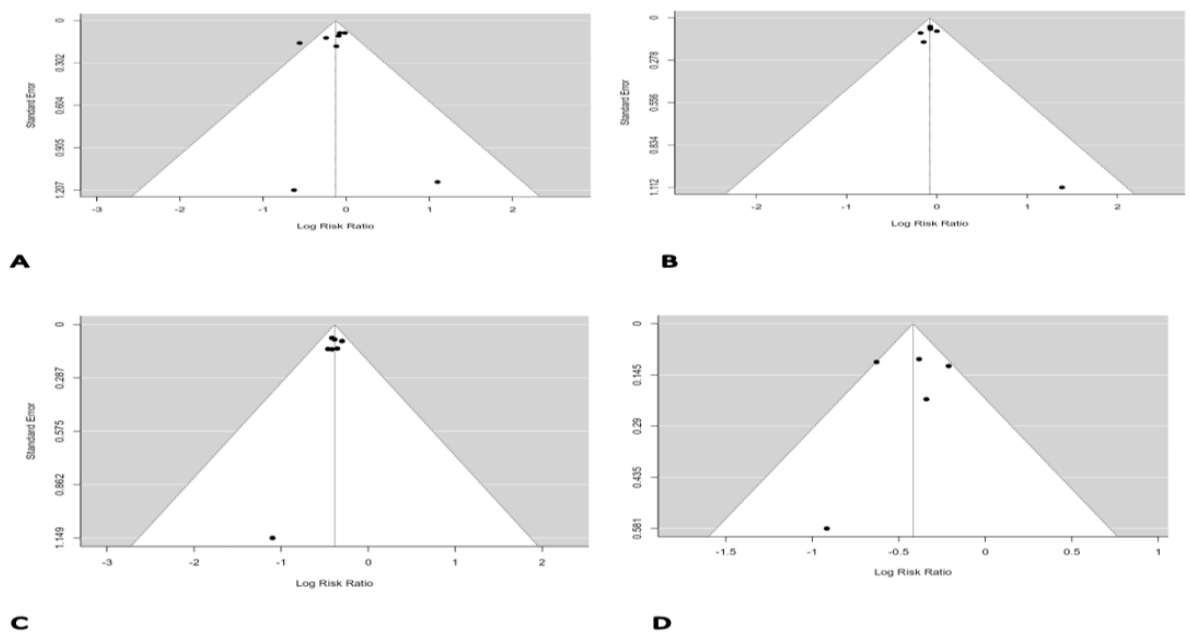

FIGURE 4: FUNNEL PLOTS SHOWS PUBLICATION BIAS ASSESSED BY EGGER'S REGRESSION TEST A) FOR CARDIOVASCULAR DEATH, B) ALL CAUSE DEATH, C) HOSPITALIZATION FOR HEART FAILURE, D) COMPOSITE RENAL OUTCOME.

DISCUSSION

This systematic review with meta-analysis has gathered and summarized up to date studies of different SGLT2 inhibitors (Dapagliflozin, canagliflozin, empagliflozin , ertugliflozin , Sota gliflozin) on cardiovascular outcome and renal disease in type 2 diabetic patients with established cardiovascular disease and moderate CKD .overall, there was significant reduction in cardiovascular death with fixed effect model -0.1482, p = 0.0008 (95% CI: -0.2345 to -0.0618), all cause death -0.1203 (95% CI: -0.1869 to -0.0536, hospitalization for heart failure -0.3851 (95% CI: -0.4623 to -0.3078) and composite renal outcome -0.4170 (95% CI: -0.5347 to -0.2994) with minimal risk of heterogeneity .But ,among this current meta-analysis, incidence of cardiovascular

death ,all cause death have shown pooled effect in favor of SGLT2 inhibitors ,but results of majority of included studies have crossed the line of null effect ,which are assumed to be not significant .Therefore, based upon pooled, SGLT2 inhibitors shows significant effect on reducing cardiovascular, all cause death but based upon each included studies the pooled effect could not be true effect . Whereas the pooled effect of hospitalization for heart failure and composite renal outcome are showing true pooled effect because majority of included studies results are not crossing line of null effect.

There are many previous meta-analyses on cardiorenal outcome of SGLT2inhibitors are conducted and published [12,13,14]. Similar search protocols from previous meta-analysis were used but difference was population choose was different in current meta-analysis. This SR with MR has extracted studies involving diabetic patients with particularly having either established cardiovascular disease (or high risk for cardiac events) and moderate CKD patients. In current meta-analysis additional up to date studies were included [7,8].
Few studies have reported that elevated UACR and reduced eGFR [10,11] are associated with high risk for cardiovascular events, heart failure, death. Among SGLT2inhibitors, studies conducted using Sota gliflozin has involved T2DM with moderate CKD with majority has albuminuria, eGFR>30ml/min/1.73m² along with established heart failure or high risk for cardiorenal outcome , specifically started Sota gliflozin soon before discharging patient with heart failure has shown greater reduction in incidence of cardiac death, all cause death, composite renal death, HHF ,which proves its protective effects on such high risk population with earlier initiation of SGLT2 inhibitors [5,6].

There are few studies which has reported that hypertension with diabetes are associated with higher risk of cardiorenal outcome because in diabetic patients vascular dysfunction is common due to elevated glucose, insulin resistant, reduction in nitric oxide, which lead to renin angiotensin activation and vascular dysfunction, which end up in hypertension. Chronic hypertension with diabetes will lead to increased collagen deposition in arteries and precipitate vascular events like stroke, myocardial infarction, chronic kidney disease [31,32]. This meta-analysis has involved majority of patients [7,8,3,4,5] with history of hypertension to evaluate the significant reduction of cardiorenal events in high risk patients.

There are few other reviews which has compared SGLT2 inhibitors with other comparators like GLP1 receptor agonist in diabetic patients with cardiovascular disease, which has shown similar and significant risk reduction in cardiac events in both group of drugs. But, SGLT2 inhibitors were shown to have significant risk reduction in patients with eGFR <60ml/min/ 1.73m² [36]. Difference between current meta-analysis and previous is, current analysis has used different comparator and involved updated studies.

There was a systematic review with meta-analysis [40] conducted in recent year, between SGLT2 inhibitors, GLP1 receptor agonist (glucagon like peptide 1), DPP-4 inhibitors (Dipeptidyl peptidase 4 inhibitors) to evaluate the risk reduction in cardiorenal outcome with or without diabetes. They have included 23 trials comparing all those drugs efficacy in reducing the cardiorenal outcome. Among them GLP1 receptor agonist and SGLT2 inhibitors have shown significant reduction in incidence of cardiorenal outcome like MACE (major adverse cardiovascular events), cardiac death, all cause death, nonfatal Myocardial infarction, nonfatal stroke,

hospitalization for heart failure and renal outcome. But, DPP4 inhibitors does not show significant reduction in incidence of cardiorenal outcome when compared to other two group of drugs. In addition, SGLT2 inhibitors shows pronounced effect in reducing incidence of hospitalization for heart failure and renal death when compared to GLP1 receptor agonist. Whereas, GLP1 receptor agonist were superior to SGLT2 inhibitors in reducing nonfatal stroke only. Similar results were [14] found in previous studies which has treated patients with combination of SGLT2 inhibitors like canagliflozin and GLP1 receptor agonist in cardiovascular risk patients. The results show greater efficacy in cardiorenal disease in SGLT2 inhibitors with GLP1 receptor agonist than patients who was not treated with GLP1 agonist, but there was no convincing explanation provided. All the three class of drugs has good efficacy with low incidence of hypoglycemia, which could be beneficial to treat even chronic kidney disease patients because they are more prone for hypoglycemia. SGLT2 inhibitors and GLP 1 agonist have weight loss as additional benefit to even use in obese patients.

This meta-analysis has shown significant reduction in cardiorenal events even in reduced eGFR patients. Such association were recently seen in meta-analysis [42] conducted by Maddaloni et al., 2023, has evaluated the cardiorenal outcome based upon eGFR subgroups, 13trials were included from RCT on SGLT2 inhibitors. They have proved that the relative risk of heart failure outcome was reduced by 13% to 32% across eGFR subgroups and progression of kidney disease was reduced by 27%to 57% with low heterogeneity. They have revealed the direct relationship of eGFR with SGLT2 inhibitors. Greater reduction of renal outcome happened in subgroup with eGFR ≥90 mL/min/1.73 m^2 and least reduction happened with eGFR <30 mL/min/1.73 m^2. To the contrary, heart failure risk reduction was more pronounced in eGFR<30 mL/min/1.73 m^2 and lowest with eGFR ≥90 mL/min/1.73 m^2. As current meta-analysis has included only moderate CKD with eGFR ≥30 mL/min/1.73 m^2 and has not done subgroup analysis based on eGFR because few studies does not mention eGFR subgroups data, we were not able provide such clarification based on baseline eGFR subgroups. But overall, the cardiac outcome shows relatively higher risk reduction than renal outcome in moderate CKD patients based upon current analysis.

There were few previous studies [5,2] which has utilized SGLT2 inhibitors like dapagliflozin and Sota gliflozin to evaluate the effectiveness of the drug in type 2 diabetic patients with stage 3a chronic kidney disease (eGFR, 40–65 mL/min/1.73 m^2). Dapagliflozin mechanism of action are based upon glomerular filtration rate as well as blood glucose levels .Therefore , these drugs were restricted to use in severe chronic renal disease patients as their glucose lowering effects were been attenuated due to severe reduction in glomerular filtration rate. But, few studies [41] have done randomized trials in type 3a chronic kidney disease patients, which has revealed that the glucose lowering effect, BP, weight loss were significant. In addition, they have also shown significant reduction in eGFR from baseline on week 24 of treatment, but they have returned back to baseline by week 27. The mechanisms behind such effect on eGFR were not clearly explained. In this current meta-analysis only one dapagliflozin study were been used, therefore separate efficacy of dapagliflozin on CKD were been difficult to comment. But, altogether SGLT2 inhibitors were showing significant cardiorenal protection even in type 2 diabetic patients with moderate CKD especially with eGFR ≥40ml/min/ 1.73m^2.

This meta-analysis has included four large cardiovascular outcome trial. Each of them was conducted with help of robust design and all the studies were proven to show low risk of bias, which will provide proper effective results upon all those four major outcomes pertaining to cardiorenal issues in diabetic patients. But, study (39) involving canagliflozin, which has given the outcome in rate of events rather than number of patients affected were not included in this meta-analysis, as it was difficult to compare with other studies included in this study. The statistical evidence for all outcome shows moderate to low heterogeneity, therefore these results can provide better guide for current guideline in management of diabetic patients with risk of cardiorenal outcome.

LIMITATION

The present meta-analysis has few limitations. Firstly, it has relatively small number of studies included for analysis, which could reduce the power required to prove the true significant effect between studies in Meta regression analysis. But, still 4 large studies have been included which are assumed to produce more likely true effect in this meta-analysis. Secondly, studies which does not provide proper data on subgroups of established cardiovascular disease based on number of patients with history of MI, Stroke, heart failure, STEMI as well as chronic kidney disease based upon albuminuria, eGFR are excluded from this analysis, which can still affect the statistical power of analysis. Thirdly, all studies were using placebo for comparison, which provide indirect comparison and can hinder confounding factors by difference in patient characteristics like pharmacological agents used against hypertension, diabetes, heart failure and kidney diseases associated with diabetes. Since , this meta-analysis has included large cardiovascular outcome; we could assume that the results of meta-analysis provide valid proof on prescribing SGLT2 inhibitor in type 2 diabetic patients with both cardiovascular disease and moderate CKD patients .But ,due to limited number of studies for analysis with above mentioned, future research and meta-analysis including more number of studies could boost up the knowledge and confidence while treating type 2 diabetic patients with both cardiovascular disease and moderate CKD.

CONCLUSION

The result of this systematic review suggest that SGLT2 inhibitors have significant efficacy in reducing the incident of cardiovascular death and composite renal outcome .This protective role of SGLT2 inhibitors in both established cardiovascular disease and moderate CKD patients are established with help of above studies which has included all the SGLT2 inhibitors (dapagliflozin, canagliflozin, ertugliflozin, Sota gliflozin, empagliflozin) .Although extent of risk of cardiorenal outcome could vary across studies based on patient, but the present evidence does not shows any particular group which was unlikely to achieve significant cardiorenal protection with SGLT2 inhibitors . Overall finding of this study, support the use of SGLT2 inhibitors in type 2 diabetic patients with cardiovascular disease and renal disease for optimizing the differential prescription to prevent major cardiovascular and renal outcome. In addition, it is also advisable to do further research especially on type 2 diabetic patients with both risk of cardiovascular disease and renal disease to find the clear mechanism and treatment strategies to reduce cardiorenal outcome.

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