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Antidiabetic Treatment with Gliptins Focus on Cardiovascular Effects and Outcomes

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ABSTRACT

Background: The occurrence of cardiovascular disease(CVD) and type 2 diabetes mellitus(T2D) is experiencing a significant increase as a result of the worldwide problem of overweight and obesity.

Aim: The objective of this systematic review and meta-analysis was to assess the effects and results of gliptins on cardiovascular system of diabetic rats.

Materials and methods: This systematic review has been done in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) statement and the criteria outlined in the Cochrane Handbook for systematic reviews of interventions. The Cochrane Risk of Bias Assessment Tool 1(ROB 1) has been utilized to evaluate the quality of the trial.

Main finding: As regard systolic Blood Pressure of studied population, our meta-analysis resulted in pooled MCs and corresponding 95% CI of ;137.1(133.9, 140.3), major heterogeneity was detected among our pooled studies with I2 and chi-p= 100%and <0.001, As regard prior CVD, our meta-analysis resulted in pooled RR and the corresponding 95% CI ; 0.7(0.5, 0.9), major heterogeneity was detected among our pooled studies with I2 and chi-p= 100%and <0.001, Figure 5; illustrated forest plot for this outcome. Heart failure was reported in five studies, our pooled meta-analysis resulted in pooled RR and corresponding 95% CI; 0.18(0.1, 0.25), major heterogeneity was detected among our pooled studies with I2 and chi-p= 100%and <0.001,

Conclusion: Gliptins or DPP-4 inhibitors provide effective glycemic control with good tolerability, particularly without severe hypoglycemia, and also offer non-glycemic benefits on CV risk factors in T2DM patients.

Keywords: Gliptins, Cardiovascular system, Effects

INTRODUCTION

As a result of the worldwide health problem of obesity and overweight, the occurrence of CVD and T2D mellitus is experiencing a significant increase. The progression of micro- & macrovascular complications, such as chronic kidney disease (CKD), stroke, blindness, & coronary artery disease (CAD), is significantly influenced by diabetes. Life expectancy is reduced by each of the 3 individual cardiovascular risk factors: a current heart attack, stroke or diabetes. The life expectancy decreases significantly further when these illnesses are combined**(1)**.

A critical risk factor for cardiovascular disease is Type 2 Diabetes. The frequency of acute thrombotic events, involving myocardial infarction (MI) and stroke, is significantly higher in diabetic cases than in non-diabetics. In the same manner , T2D is linked to a worse prognosis after myocardial infarction, which increases the possibility of heart failure (HF) and death during long-term monitoring **(2)**.

The possibility of heart failure is greater in diabetic cases compared to those with euglycemia. In recent decades, a significant bidirectional connection among diabetic cases and cardiac disease has been demonstrated in a variety of randomized investigations. Through numerous mechanisms that result in vascular injury as a consequence of long-term hyperglycemia, hyperglycemia has been recognized as an independent risk factor for ischemic heart disease (IHD) **(3)**.

The management of hyperglycemia must address a variety of organ defects, including impaired muscular and hepatic insulin resistance, decreased intestinal-driven incretin effect, pancreatic insulin production, and a raised glucose kidney threshold. Therefore, it is frequent for a combination of glucose-lowering compounds with complementary modes of action to be necessary in order to achieve optimal glucose control in T2DM **(4)**.

The gliptins, additionally referred to as dipeptidyl peptidase-4 (DPP4) inhibitors, are a group of antidiabetic compounds that have been in growing usage globally since the FDA approved the 1st of them, sitagliptin, in 2006 **(5)**.

Therefore, this systematic review & meta-analysis evaluated the effects and outcomes gliptins on cardiovascular system of diabetic rats.

MATERIALS AND METHODS

It is important to note that this systematic review was done in compliance with the Preferred Reporting Items for Systematic Reviews & Meta-Analyses statement as well as the criteria that are defined in the Cochrane Handbook for systematic reviews of treatments.

PICOs: A specific question has been structured with regard to the population, intervention, comparison and outcomes (PICOs) approach. The PICOs questions has been defined as follows: Population (P): Diabetic rodents; Intervention (I): Gliptins; Comparison (C): Other diabetic treatments; Outcome (O): Cardiovascular system effects; and Research (s) design: In vitro and in vivo investigations. The current systematic review has been conducted to investigate whether the cardiovascular system is impacted by antidiabetic management with gliptins.

Search Strategy: The search has been conducted in the following databases: the Cochrane Library, Web of Science, and MEDLINE (PubMed).

Eligibility criteria: Inclusion criteria for investigations were as follows: (a) in vitro and in vivo investigations; (b) research that investigated diabetic rodents; and (c) investigations that assessed the impact of **gliptins on the cardiovascular system of diabetic rats**. The following criteria were utilized to exclude research that met one or more of the following: a) research that do not utilize gliptins; b) reviews, protocols, or guidelines; and c) research that are obsolete.

Data extraction: A standardized form in Microsoft Excel has been utilized by two evaluators to carry out data extraction independently and in duplicate. The authors and publication year, intervention, sample size, and design of investigation were all extracted from the complete text of the included articles.

Risk of bias assessment

The Cochrane Risk of Bias assessment tool 1 (ROB 1), which has been developed particularly for interventional research, has been utilized to evaluate the quality of the trial. Detection bias, attrition bias, performance bias, reporting bias, Selection biasand prospective sources of bias are all included in this evaluation instrument. The level of bias in each trial was analyzed, and the researchers classified it as "high," "low," or "unclear" for each parameter under consideration.

Data synthesis

In order to aggregate the mean changes (MCs) for our constant evaluated results with their corresponding ninety-five percent confidence intervals (CIs), we carried out a single-arm meta-analysis. If the effect evaluate has been aggregated from homogeneous investigations, the fixed effect model has been initially implemented; otherwise, the random effect model has been applied. Utilizing the I2 statistics Chi2-P test, we examined the statistical heterogeneity between investigations. Outcomes with a Chi2-p value of greater than 0.1 were deemed heterogeneous, while I2 values of over fifty percent suggested high heterogeneity. All statistical analyses have been conducted utilizing Open-Meta Analyst software.

RESULTS

Literature Search: In our initial search across databases, we recognized 388 investigations. After eliminating duplicate investigation, we were left with 98 articles that required further assessment of their abstracts and titles. This process resulted in the identification of fourteen investigations that demonstrated possible relevance and have been subsequently exposed to a comprehensive full-text assessment. Five of these investigations were ultimately consistent with our predetermined inclusion criteria. This selection process is demonstrated in the PRISMA flowchart in **Figure 1**.

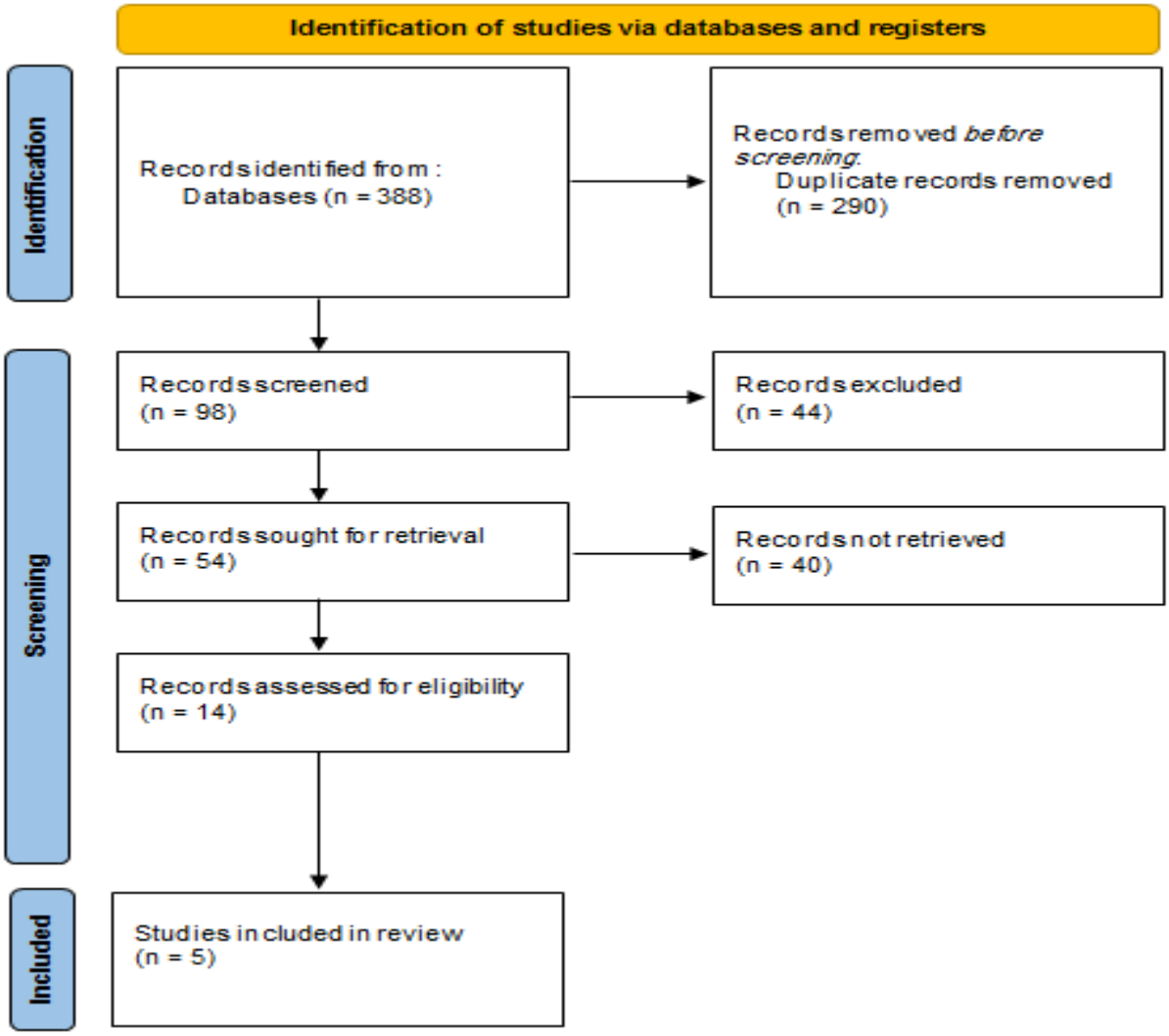


Figure 1: PRISMA flow chart for investigation selection process.

Table 1: baseline characteristics for involved investigations.

Study ID	study design	sample size female %	follow up in years	Age mean(SD)	BMI	HbA1c mean(SD)	Diabetes duration years	SBP mmHg Mean(SD)
White (6)	RCTs	5380 (32.1%)	1.5	61(10)	28.3	8(1.1)	7.2	83.10%
Scirica (7)	RCTs	16490 (27.2%)	2.1	65.1(8.5)	31.2	8(1.4)	10.3	81.80%
Green (8)	RCTs	14671 (29.3%)	3	65.5(8)	30.2	7.2(0.5)	11.6	135(17)
Rosenstock (9)	RCTs	6979 (37.1%)	2.2	65.9(9.1)	31.4	8(1)	14.7	140.5(17.9)
Rosenstock (10)	RCTs	6033 (40%)	6.3	64(9.5)	30.1	7.2(0.6)	6.3	136(16)

Risk of bias assessment

Most of our involved RCTs illustrated good quality other studies showed fair Quality by ROB1 tool the most biased domains were attrition bias and reporting bias. Risk of bias graph & summary were illustrated in figure 2 and Table 2.

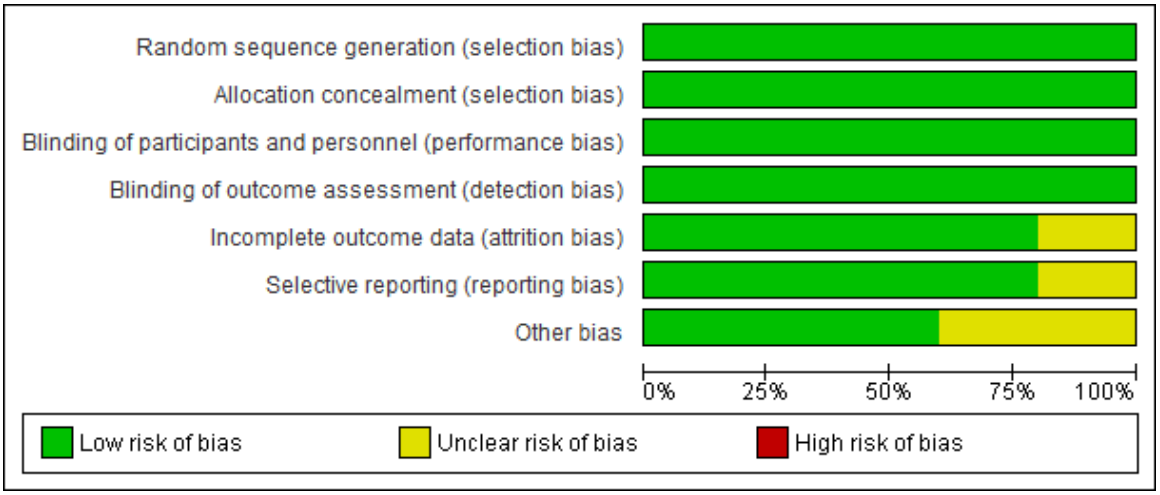
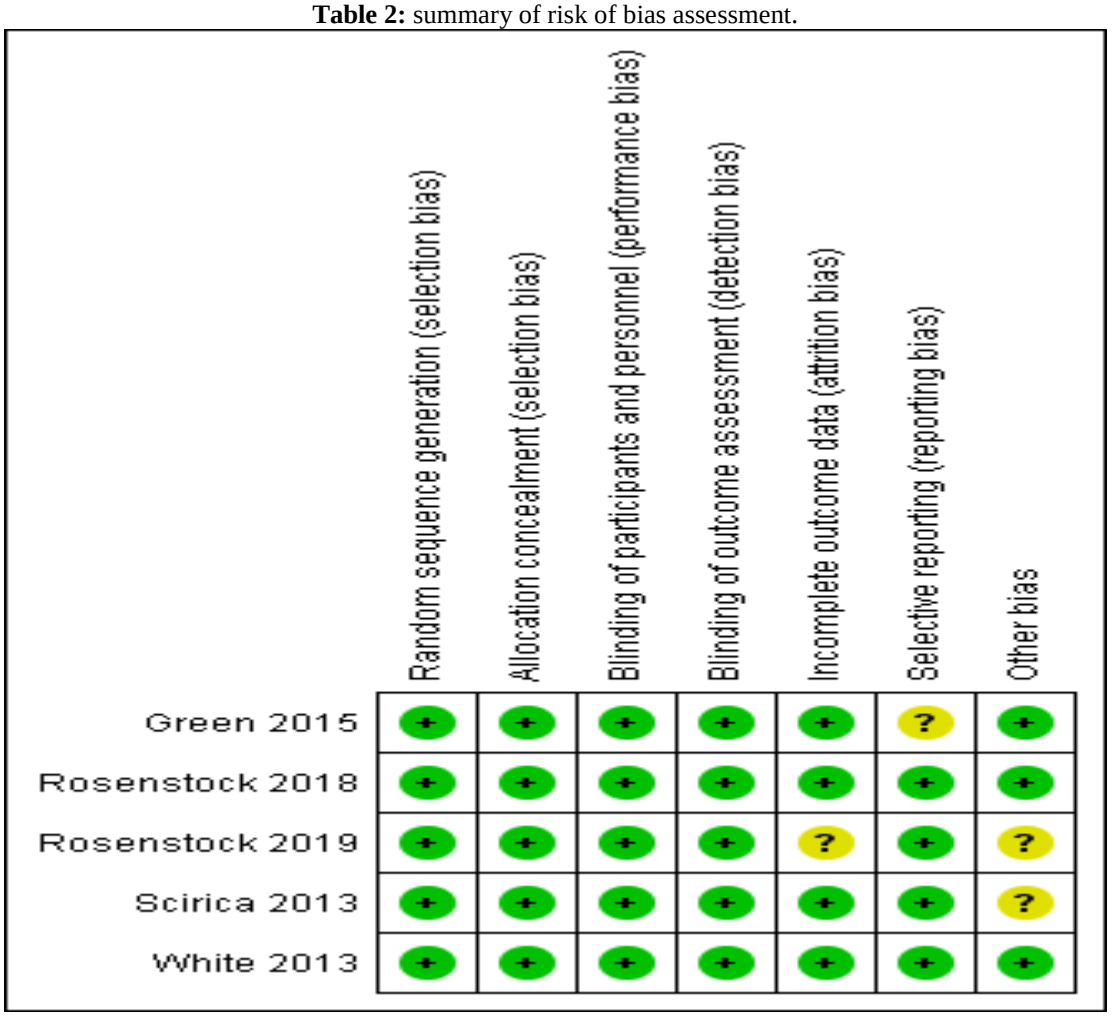


Figure 2: Risk of bias graph.

Table 2: summary of risk of bias assessment.



Outcomes

1.HbA1c

For HbA1c of studied population, our meta-analysis resulted in pooled MCs and corresponding 95% CI ;7.6(7.3, 8), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001, **Figure 3;** illustrated forest plot for this outcome.

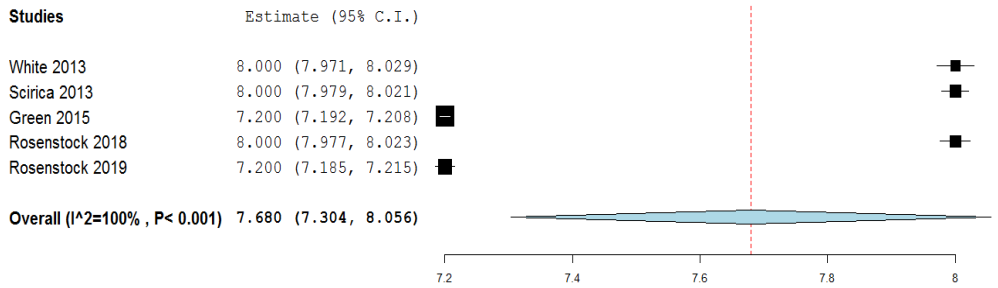


Figure 3: forest plot for HbA1c.

2-SBP mmHg

As regard systolic Blood Pressure of studied population, our meta-analysis resulted in pooled MCs and corresponding 95% CI of ;137.1(133.9, 140.3), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001, Figure 4; illustrated forest plot for this outcome.

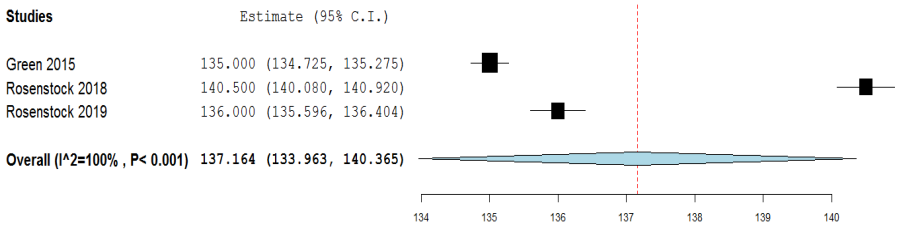


Figure 4: forest plot for SBP in mmHg.

3.Prior CVD

As regard prior CVD, our meta-analysis resulted in pooled RR and the corresponding 95% CI ; 0.7(0.5, 0.9), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001, **Figure 5;** illustrated forest plot for this outcome.

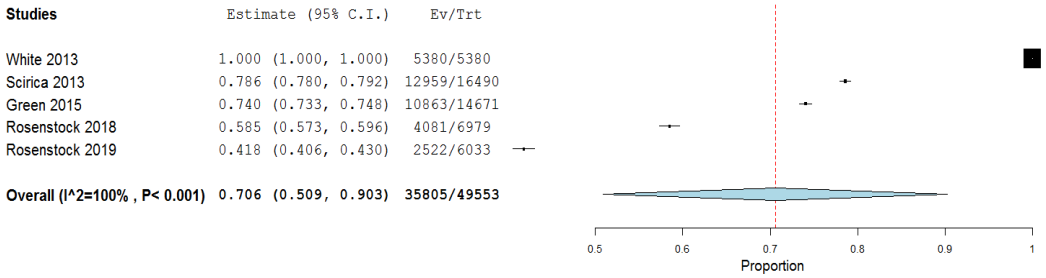


Figure 5: forest plot for prior CVD.

4.Heart failure

Heart failure was reported in five studies, our pooled meta-analysis resulted in pooled RR and corresponding 95% CI ; 0.18(0.1, 0.25), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001, **Figure 6;** illustrated forest plot for this reults.

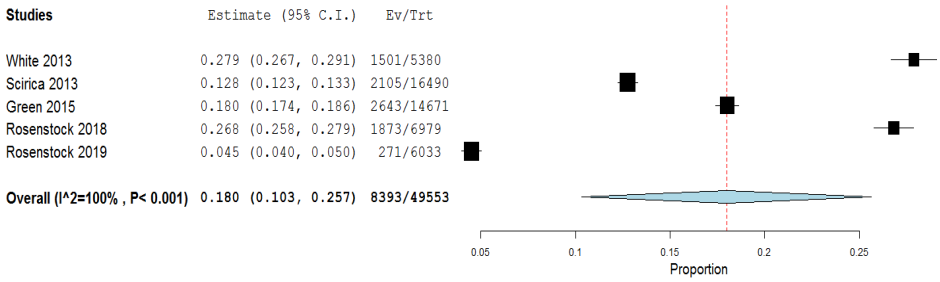


Figure 6: forest plot for Heart failure.

5.eGFR 60ml/min

our pooled meta-analysis for estimated GFR resulted in 0.29(0.15,0.43), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001, Figure 7; illustrated forest plot for this findings.

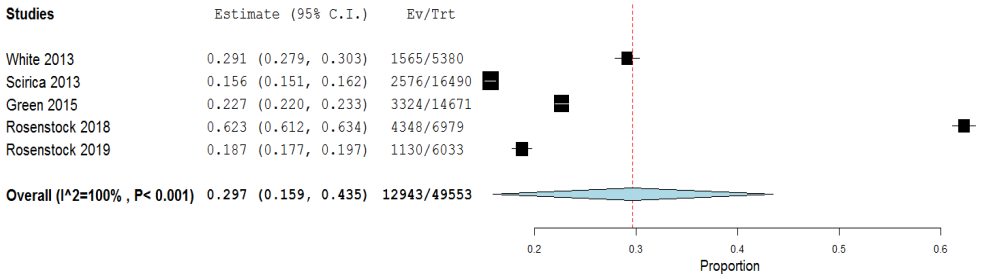


Figure 7: forest plot for eGFR 60ml/min.

DISCUSSION

A promising pharmacological class of glucose-lowering compounds, dipeptidyl peptidase inhibitors, are frequently referred to as gliptins. They offer new perspectives for treatment of T2DM. Incretins, including glucagon-like peptide 1 (GLP-1), are degraded by the DPP-4 enzyme, which is responsible for secretion of glucose-dependent insulin from pancreas. There are currently numerous commercially available dipeptidyl peptidase 4 inhibitors. alogliptin, saxagliptin, , vildagliptin, sitagliptin, and linagliptinamong others, are currently under development **(11, 12)**.

Our meta-analysis included approximately 49553 cases from five investigations. All our investigation, were RCTs. The monitoring periods of the investigations our review included varied from 1.5 years to six years, and the BMI varied from 28 to 31.

Risk of bias assessment

Most of our involved RCTs illustrated good quality other studies showed fair Quality by ROB1 tool the most biased domains were attrition bias and reporting bias **(6-10)**.

Outcomes

For HbA1c: our meta-analysis resulted in pooled MCs and corresponding 95% CI ;7.6(7.3, 8), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100% and <0.001. (6-10).

White et al. (6) conducted a study to ascertain whether alogliptin is noninferior to placebo in terms of major cardiovascular events in cases who have T2D who are at elevated risk and have recently experienced acute coronary syndromes. The study determined that the mean glycated hemoglobin in the alogliptin group was 8.0±1.1 at baseline, while the mean glycated hemoglobin in the placebo group was 8.0±1. The alogliptin group experienced a mean variation from the baseline of -0.33%, while the placebo group experienced a mean change of -0.03%. The least-squares mean distinction among the alogliptin group & the placebo group was -0.36 percentage points (ninety-five percent CI, -0.43 to -0.28; P-value less than 0.001).

Scirica et al. (7) carried out an investigation to assess both the safety and efficiency of saxagliptin in cases who have diabetes mellitus who are at danger for CV events. They found that the mean glycated hemoglobin in the saxagliptin group was 8.0±1.4 at baseline, while the mean glycated hemoglobin in the placebo group was 8.0±1.4. However, the levels of glycated hemoglobin in the saxagliptin group were significantly lower in comparison with those in the placebo group at one year (7.6percent vs. 7.9percennt), 2 years (7.5percent vs. 7.8percent), and the end of the management period (7.7percent vs. 7.9percent) (P-value less than 0.001 for all comparisons).

For systolic blood: our meta-analysis resulted in pooled MCs and corresponding 95% CI of ;137.1(133.9, 140.3), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100% and <0.001 (8-10).

Rosenstock et al., (9) conducted a study to assess the impact of linagliptin, a selective dipeptidyl peptidase -4 inhibitor, on CV and renal results in cases who have T2D who were at an elevated possibility of CV and renal events. The study found that the mean systolic blood pressure in the linagliptin group was 140.4 +/-17.7 at baseline, while the mean systolic blood pressure in the placebo group was 140.6 +/-18. Following therapy, there were no variances in systolic blood pressure among the groups.

For prior CVD: our meta-analysis resulted in pooled RR and the corresponding 95% CI; 0.7(0.5, 0.9), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001 (6-10).

Green et al. (8), who aimed to ascertain whether sitagliptin was noninferior to placebo, discovered that the 1^{ry} composite cardiovascular result happened in 839 cases in the sitagliptin group (11.4 percent) & 851 cases in the placebo group (11.6 percent) in the intention-to-treat population. In the 1^{ry} composite cardiovascular result, there

was an insignificant distinction between the groups (P-value equal 0.84 superiority). Also, in agreement with Scirica et al. (7), they stated that a 1^{ry} end-point event of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke happened in 613 cases in the saxagliptin group (7.3percent) and in 609 cases in the placebo group (7.2percent) (hazard ratio, 1.00; ninety-five percent CI, 0.89 to 1.12; P-value equal 0.99 for superiority and P-value less than 0.001 for noninferiority). As well agreed with Rosenstock et al., (9)they found that there 57% had established CV disease.

For Heart failure: our pooled meta-analysis resulted in pooled RR and corresponding 95% CI; 0.18(0.1, 0.25), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001 (6-10).

Green et al. (8) discovered that the incidence of hospitalization for heart failure didn't vary significantly at 2^{ry} results. Additionally, the composite result of cardiovascular death or heart failure didn't exhibit a statistically significant distinction (p value = 0.74). This outcomes was in line with the findings of Scirica et al. (7) & White et al. (6), who discovered that Sitagliptin therapy didn't result in alterations in the rates ofhospitalization for heart failure, as has been indicated in trials of other dipeptidyl peptidase -4 inhibitors. The rate of the composite result of hospitalization for heart failure or cardiovascular death didn't differ among the groups.

For estimated GFR: our pooled meta-analysis resulted in 0.29(0.15,0.43), major heterogeneity was detected among our pooled studies with I^2 and chi-p= 100%and <0.001 (6-10).

Green et al. (8) showed that the sitagliptin group experienced a greater mean alteration from baseline in the eGFR than the placebo group at forty-eight months (−4.0±18.4 and −2.8±18.3 milliliters per minute per 1.73-meter square, correspondingly). The sitagliptin group maintained a slightly lower eGFR throughout all post-randomization visits, with an estimated least-squares mean distinction of −1.34 milliliters per minute per 1.73-meter square (ninety-five percent CI, −1.76 to −0.91; P-value equal 0.001). Additionally, Rosenstock et al. (9) determined that there was statistically insignificant variance among the Linagliptin group and the Placebo group at baseline, as well as in the 1^{ry}, 2^{ry}, and exploratory results, as indicated by the p value equal 87.

CONCLUSION

Gliptins or DPP-4 inhibitors have been illustrated to provide consistent and efficient glycemic control with a favorable tolerability profile, particularly in the absence of severe hypoglycemia, as evidenced by a multitude of clinical trials. Cases with T2DM have additionally observed additional non-glycemic favorable effects on certain well-known CV risk factors.

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