

Efficacy and Safety of Novel Dipeptidyl-Peptidase-4 Inhibitor Evogliptin in the Management of Type 2 Diabetes Mellitus: A Meta-Analysis

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Abstract

Aims: No meta-analysis is available which has summarized and holistically analyzed the efficacy and safety of evogliptin. We undertook this meta-analysis to address this gap in knowledge. **Methods:** Electronic databases were searched for RCTs involving diabetes patients receiving evogliptin in intervention arm and placebo/active comparator in control arm. Primary outcome was to evaluate changes in HbA1c. Secondary outcomes were to evaluate alterations in fasting glucose, postprandial glucose, lipids, insulin resistance, patients achieving glycemic targets of HbA1c <7% and <6.5%, and adverse events. **Results:** From initially screened 57 articles, data from six RCTs involving 887 patients was analyzed [three having sitagliptin/linagliptin as active comparator; three having placebo in control group]. Evogliptin was noninferior to sitagliptin/linagliptin regarding HbA1c reduction at 12 weeks [mean difference (MD) -0.06%; 95%CI: -0.23–0.11%; $P = 0.48$] and 24 weeks (MD 0.04%; 95%CI: -0.11–0.19%; $P = 0.60$) follow-up. Evogliptin was superior to placebo regarding HbA1c reduction at 12-weeks (MD -0.57%; 95%CI: -0.62– -0.52%; $P < 0.001$) and 24 weeks (MD -0.28%; 95%CI: -0.47 – -0.09%; $P = 0.004$). Evogliptin was noninferior to sitagliptin/linagliptin regarding patients achieving HbA1c <7% and <6.5% at 12 weeks and 24 weeks follow-up. Total adverse events [Risk ratio (RR) 0.98; 95% CI: 0.72–1.32; $P = 0.89$] and severe adverse events (RR 0.65; 95% CI: 0.25–1.67; $P = 0.37$) were not significantly different among groups. Patients receiving evogliptin did not have increased symptomatic (RR 0.46; 95% CI: 0.10–2.16; $P = 0.32$) and asymptomatic (RR 1.09; 95% CI: 0.61–1.97; $P = 0.77$) hypoglycaemia. **Conclusion:** Evogliptin is well tolerated and has good glycemic efficacy over 6 months use for T2DM management

Keywords: Evogliptin, glycemic efficacy, meta-analysis, safety, type 2 diabetes mellitus

INTRODUCTION

Evogliptin, a novel, highly selective dipeptidyl-peptidase-4 inhibitor (DPP4i) was first approved for clinical use in South Korea in October, 2015.^[1] In India, it is available for management of type 2 diabetes mellitus (T2DM), since its approval in August 2018. Owing to its long half-life of 33 h, it is dosed at 5 mg once daily.^[2] It causes a sustained inhibition of more than 80% of the enzyme activity, by interacting with the S₂-extensive subsite of the dipeptidyl-peptidase-4(DPP4) enzyme's active site. This occurs within one hour of ingestion and remains sustained over 24 h at the recommended dosage of 5 mg once daily.^[3,4] There is a resulting 1.5- to 2.4-fold increase in the postprandial active glucagon-like peptide-1 levels, with

an effective postprandial plasma glucose (PPG) reduction by 25–35%.^[4] It is believed that dose adjustment is not warranted in the presence of diabetes kidney disease, as the drug predominantly undergoes hepatic metabolism via CYP3A4.^[4,5] Clinical trials from different parts of the globe (Korea, UK, Brazil and India) have reported good glycemic efficacy of

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evogliptin in T2DM.^[6] However literature search reveals that till date, there is no meta-analysis of the clinical efficacy and safety of this novel DPP4i. We undertook this meta-analysis to address this gap in knowledge.

METHODS

This meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the filled checklist of which can be found at the end of the manuscript.^[7] The predefined protocol has been submitted for registration in PROSPERO having registration number of CRD42020190459. As ethical approval already exists for individual studies included in the meta-analysis, no separate approval was required for this study.

The PICOS criteria were used to screen and select the studies for this meta-analysis with patients (P) being people living with T2DM; intervention (I) being use of evogliptin for managing T2DM; control (C) being patients either on placebo or any other approved medication for managing T2DM; outcomes (O) being evaluated were impact on HbA1c, fasting plasma glucose (FPG), PPG, and adverse events. Only patients with T2DM were considered for this meta-analysis. Patients with other forms of diabetes were excluded. Only those studies with at least two treatment groups, with one of the group receiving evogliptin either alone or a part of standard diabetes treatment regimen (SDTR) and the other group receiving placebo or another DPP4 inhibitor, either alone or as a part of SDTR were included.

The primary outcome was to evaluate the changes in HbA1c. The secondary outcomes were to evaluate the alterations in FPG, percentage of patients achieving glycemic targets of HbA1c <7% and <6.5%, changes in lipid parameters, insulin resistance parameters (HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; QUICKI: Quantitative insulin sensitivity check index), discontinuation of medication due to adverse events, and any other adverse events as described by authors. Analysis was done based on whether the control group received an active comparator (usually another DPP4 inhibitor) – labeled here as the active control group (ACG) or a placebo – labeled as passive control group (PCG).

Search method for identification of studies

A detailed electronic databases of Medline (Via PubMed), Embase (via Ovid SP), Cochrane central register of controlled trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health, and Google scholar were searched using a Boolean search strategy: (evogliptin) AND (diabetes).

Data extraction and study selection

Data extraction was carried out independently by two authors using standard data extraction forms. In cases where more than one publication of a single study group were found, results were grouped together and relevant data from each report were used

in the analyses. Data on the primary and secondary outcomes as stated above was extracted. Patient characteristics (including demographic information and comorbidities) from the different studies included in the analysis were noted in a tabular form [Table 1]. All disagreements were resolved by the third and fourth authors.

Assessment of risk of bias in included studies

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman) Version 5.3 (The Cochrane Collaboration, Oxford, UK 2014) software. The following points were taken into consideration. Selection bias (adequate sequence generation and allocation concealment) was assessed. It was analyzed whether or not the knowledge of the allocated interventions was adequately prevented during the study. Participants and personnel (performance bias) blinding was specifically evaluated as was the blinding of the outcome assessors (detection bias). It was also assessed whether or not the incomplete outcome data issue was adequately addressed (attrition bias) and if reports of the study were free of suggestion of selective outcome reporting (reporting bias). Lastly, it was evaluated if the study was apparently free of other problems that could put it at a risk of bias. Any disagreements were resolved by the fourth author.

Measures of treatment effect

For continuous variables, the outcomes were expressed as mean differences (MD). Conventional units were used for analysis, and all studies reporting results in SI units were converted to conventional units for analysis. For dichotomous outcomes (treatment success) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). For adverse events, results were expressed as post treatment absolute risk differences. RevMan 5.3 was used for comparing MD of the different primary and secondary outcomes between the evogliptin and the control groups of the included studies.

Dealing with missing data

Any additional information required from the original authors were requested by written e-mail correspondence and any relevant information thus obtained were included in the meta-analysis. Evaluation of important numerical data such as screened and randomized people as well as intention-to-treat, as-treated and per-protocol populations were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated.

Assessment of heterogeneity

Heterogeneity was initially assessed by studying the forest plot generated for the primary and secondary outcomes of this study. Subsequently heterogeneity was analyzed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test.^[8] The interpretation of I² values is as follows: 0–40%: might not be important; 30–60%: may represent

Table 1: Patients characteristics of randomized controlled trials on use of evogliptin in type-2 diabetes in this meta-analysis (Ref)

	Ajmani	Cercato	Hong	Kim	Park	Jung
Type of study	Randomized, double-blind, double-dummy, active-controlled, parallel group, multicenter study	Multicentric, randomized, double-dummy, parallel study	Randomized, double-blind, active-controlled, parallel-group, multi-center, dose-confirmatory study.	Multicenter, randomized, double-blind, active-controlled,	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase III study,	Phase II, multicenter, randomized, double-blind, placebo-controlled study.
Study Place	18 centers across India	10 Brazilian sites	24 university hospitals throughout Korea	19 different sites in Korea	25 sites in Korea	26 university hospitals throughout Korea
Year of publication	2019	2019	2016	2020	2017	2015
Study duration	24 weeks	12 weeks	24 weeks followed by open label extension arm with evogliptin 5 mg for 52 weeks	12 weeks followed by 12 weeks open-label extension study	24 week	12 week
No. in Evogliptin/Control group	E-75/S-75	E 2.5-25 E 5-36 E 10-36 S-39	E-112 S-110	E-100 L-104	E-78 P-80	E 2.5-40 E 5-43 E 10-37 S-38
Inclusion criteria	T2DM aged 18-65 years with inadequate glycemic control (7% ≤ HbA1c <10%) after receiving at least 8 weeks of stable metformin monotherapy (≥1 g/day), were enrolled in this study.	Patients aged 20 to 75 years, with 7.5% ≤ HbA1c ≤10.5% at screening, BMI between 20 kg/m ² and 40 kg/m ² (lim- its included), and who had not been on any hypoglycemic agent within 12 weeks prior to screening	Age 18 years and older with T2DM with inadequate glycemic control (6.5% ≤ HbA1c <11.0%) with metformin monotherapy for more than 12 weeks and metformin ≥1000 mg daily for more than 6 weeks. Additional criterion 20.0 kg/m ² ≤ BMI ≤40.0 kg/m ² .	Age ≥20 years, diagnosed with T2DM with HbA1c level ≥7.0% and ≤10.0%, with a BMI ≥20 kg/m ² and ≤40 kg/m ² , and not been prescribed any hypoglycemic medication within the recent 8 weeks.	Age ≥18 years and had not received any antidiabetic agents for 6 weeks prior to the screening. The patients were required to have FPG levels <15.0 mmol/L and HbA1c levels of 6.5% to 10% at the screening and at week-2.	Age 20 and 75 years with HbA1c range of 7.0-10.0% who were diagnosed with T2DM for the first time in 4 weeks prior to screening or HbA1c in the range of 7.0-10.0% who had not been treated with OHAs in the 6 weeks prior to screening.
Age (years)	E 49.3±7.55 S 51.4±8.79	E2.5-50.46±9.33 E5-53.17±11.5 E10-50.11±9.36 S-52.1±10.41	E-57.6±9.4 S-57.3±9.3	E-56.6±10.7 L-55.6±10.2	E-57.6±11.0 P-56.8±9.8	E2.5-52.10±11.48 E5-54.2±9.74 E10-53.1±9.6 P-54.42±9.85
Sex	52.7/47.3%	E2.5-54.3/45.7% E5-47.2/52.8% E 10-47.2/52.8% S-53.4/46.2%	E-45.5/54.5% S-47.3/53.7%	E-59.8/40.2% L-55.6/43.4%	E-48.8/51.2% P-57.5/42.5%	E2.5-55/45% E5-58.1/51.9% E 10-54/46% P -68.4/31.2%
Evogliptin group	Evogliptin 5 mg once daily	E-2.5/5/10 mg once daily	Evogliptin 5 mg once daily	Evogliptin 5 mg once daily	Evogliptin 5 mg once daily	E-2.5/5/10 mg once daily
Control group	Sitagliptin 100 mg once daily	Sitagliptin 100 mg once daily	Sitagliptin 100 mg once daily	Linagliptin 5 mg once daily	Placebo	Placebo

Contd...

Table 1: Contd...

	Ajmani	Cercato	Hong	Kim	Park	Jung
Outcome	Efficacy measures (FPG, PPG, and HbA1c) and safety measures (urinalysis, hematology, and serum chemistry) were assessed at screening, randomization, week 12, and week 24.	The primary endpoint was change in HbA1c (%) from baseline (screening) to Week 12. Other efficacy endpoints included change from baseline in FPG (mg/dL) and body weight, response rate (HbA1c <7.0% or HbA1c <6.5%) at the end of the study treatment (Week 12). Safety was evaluated by means of AEs reporting and vital signs, physical exam findings, electrocardiogram and laboratory tests (hematology, chemistry and urinalysis).	Primary efficacy endpoint-change in HbA1c at week 24. The secondary efficacy endpoints-change in HbA1c from baseline to week 52, HbA1c response rate (HbA1c<6.5%), rescue therapy rate, changes in FPG, lipid parameters (TC, LDL-C, HDL-C, TG, FFA), body weight, fasting insulin, C-peptide, HOMA-β, HOMA-IR, QUICKI and MDG at week 24 and week 52. Safety and tolerability by vital signs, laboratory measurements (including serum chemistry, hematology and urinalysis), and ECG.	The primary efficacy endpoint was the change from baseline HbA1c at week 12. The secondary endpoint was the change in the mean amplitude of glyceric excursion (MAGE) assessed by continuous glucose monitoring.	The primary efficacy endpoint-change in HbA1c from baseline to week 24. Secondary efficacy endpoints-proportion of patients achieving HbA1c <6.5% and the change in FPG from baseline. Exploratory endpoints-changes in body weight and body fat, TC, LDL, HDL, Tg, FFA, fasting C-peptide, insulin, proinsulin, GLP1, GIP; changes in HOMA-β index, HOMA-IR index, QUICKI, proinsulin/insulin ratio and insulinogenic index; changes in 2-hour glucose, C-peptide, insulin, proinsulin, GLP-1 and GIP during OGT. AEs	The primary endpoint -change in HbA1c from baseline to week 12. The secondary endpoints-HbA1c response rate [<7.0% or <6.5%], changes in FPG, glycated albumin (GA), fasting insulin, fasting proinsulin, the proinsulin/insulin ratio, fasting lipid parameters, including TC, LDL-C, HDL-C, and TG; and changes in HOMA-IR, HOMA-β, QUICKI. Safety endpoints included AEs, vital signs and laboratory test results

T2DM=type 2 diabetes mellitus, E=evogliptin, S=sitagliptin, SDC=standard diabetes care, FPG=fasting plasma glucose, PPG=postprandial glucose, BMI=body mass index, AE=adverse event, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, Tg=triglyceride, FFA=free fatty acid, HOMA=homeostatic model assessment, IR=insulin resistance, QUICKI=quantitative insulin-sensitivity check index, MDG=mean daily glucose, L=linagliptin, GLP1=glucagon-like peptide-1, GIP=gastric inhibitory polypeptide, OGT=oral glucose tolerance test, OHA=oral hypoglycemic agent

moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75P–100%: considerable heterogeneity. The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of the evidence for heterogeneity (e.g., P value from the Chi^2 test, or a CI for I^2).^[8]

Grading of the results

An overall grading of the evidence related to each of the primary and secondary outcomes of the meta-analysis was done using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach.^[9] The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.^[9] The GRADEpro Guideline Development Tool software (McMaster University and Evidence Prime Inc, 2015) was used to create the Summary of Findings (SoF) table in this meta-analysis [Table 3]. Publication bias was assessed by plotting the Funnel Plot, which specifically targets small study bias, in which small studies tend to show larger estimates of effects and greater variability than larger studies.^[8] The presence of one or more of the smaller studies outside the inverted funnel plot was taken as an evidence of presence of significant publication bias.^[9]

Data synthesis

Data was pooled as random effect model for the analysis of primary and secondary outcomes. The outcomes were expressed as 95% confidence intervals (95%CI). Forrest plots were plotted using RevMan 5.3 software, with left side of the graph favoring evogliptin and right side of the graph favoring control. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 57 articles were found after the initial search [Figure 1]. Following screening of the titles, abstracts, followed by full-texts, the search was reduced down to 11 RCTs, which were evaluated for inclusion in this meta-analysis [Figure 1]. Six RCTs in people with T2DM which fulfilled all criteria were analyzed in this meta-analysis.^[6,10-14] Five RCTs were excluded as they evaluated the pharmacokinetic and pharmacodynamic properties of evogliptin.^[4,15-18]

Of the six RCTs included in this meta-analysis, RCTs by Cercato *et al.*, Ajmani *et al.*, and Hong *et al.* had sitagliptin as active control and that by Kim *et al.* had linagliptin.^[6,10-12] Hence, the data from these studies have been analyzed separately as ACG. RCTs by Park *et al.* and Jung *et al.* had placebo in the control group and hence were grouped and analyzed in the PCG.^[13,14] The details of all the RCTs included in this meta-analysis have been elaborated in Table 1.

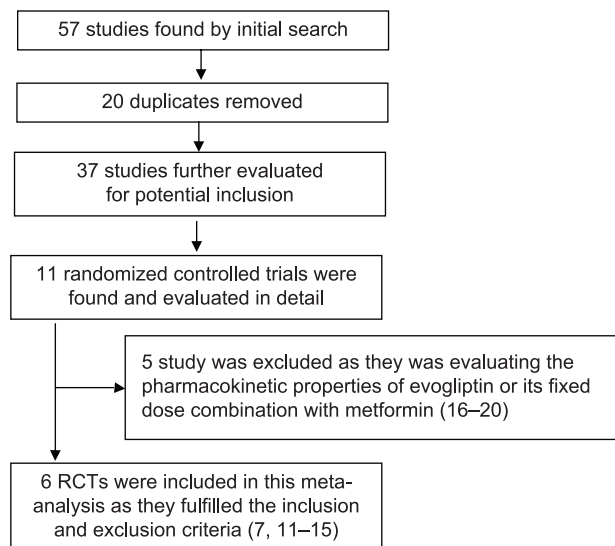


Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. RCT: randomized controlled trial

Risk of bias in the included studies

The summaries of risk of bias of the six studies included in the meta-analysis have been elaborated in Figure 2a and b. Random sequence generation, performance bias, detection bias, attrition bias, and reporting bias were judged to be at low risk of bias in all the six studies (100%). Allocation concealment (selection bias) was at low risk in four out of six studies (66.67%). In two of the studies, the nature of selection bias was not clear. Source of funding, especially pharmaceutical, authors from the pharmaceutical organizations and conflict of interests were looked into the “other bias” section. Other bias was judged to be at low risk in only one out of the six studies (16.67%) [Figures 2 and 3]. The glycemic outcomes have been separately analyzed for 12 and 24 weeks follow-up, as per the available data.

Effect of evogliptin on primary outcomes

Glycated Haemoglobin

Four studies with 506 patients analyzed the impact of evogliptin on HbA1c after 12 weeks and 3 studies with 514 patients assessed it at 24 weeks of follow-up. When compared to the ACG, evogliptin was noninferior to sitagliptin/linagliptin with regards to HbA1c reduction at 12 weeks [MD -0.06% (95% CI: -0.23–0.11%); $P = 0.48$; $I^2 = 0\%$ (low heterogeneity); Figure 3a; moderate certainty of evidence (MCE)] and 24 weeks of follow-up [MD 0.04% (95% CI: -0.11 – 0.19%); $P = 0.60$; $I^2 = 0\%$ (low heterogeneity); Figure 4a; high certainty of evidence (HCE)].

Similar analysis was not possible for evogliptin compared to PCG as data was available only from one study at 12 weeks of follow-up (Jung *et al.*, 2015) and 24 weeks of follow-up (Park *et al.* 2017). Analysis of data from these studies revealed evogliptin was superior to placebo with regards to HbA1c reduction at 12 weeks [MD -0.57% (95% CI: -0.62 – -0.52%);

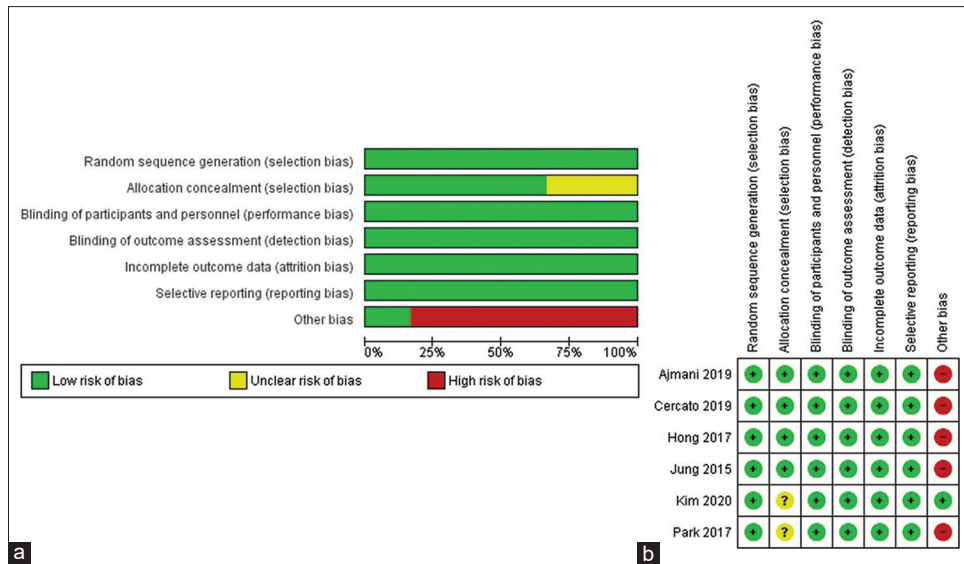


Figure 2: (a): Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies; (b): risk of bias summary: review authors' judgments about each risk of bias item for each included study

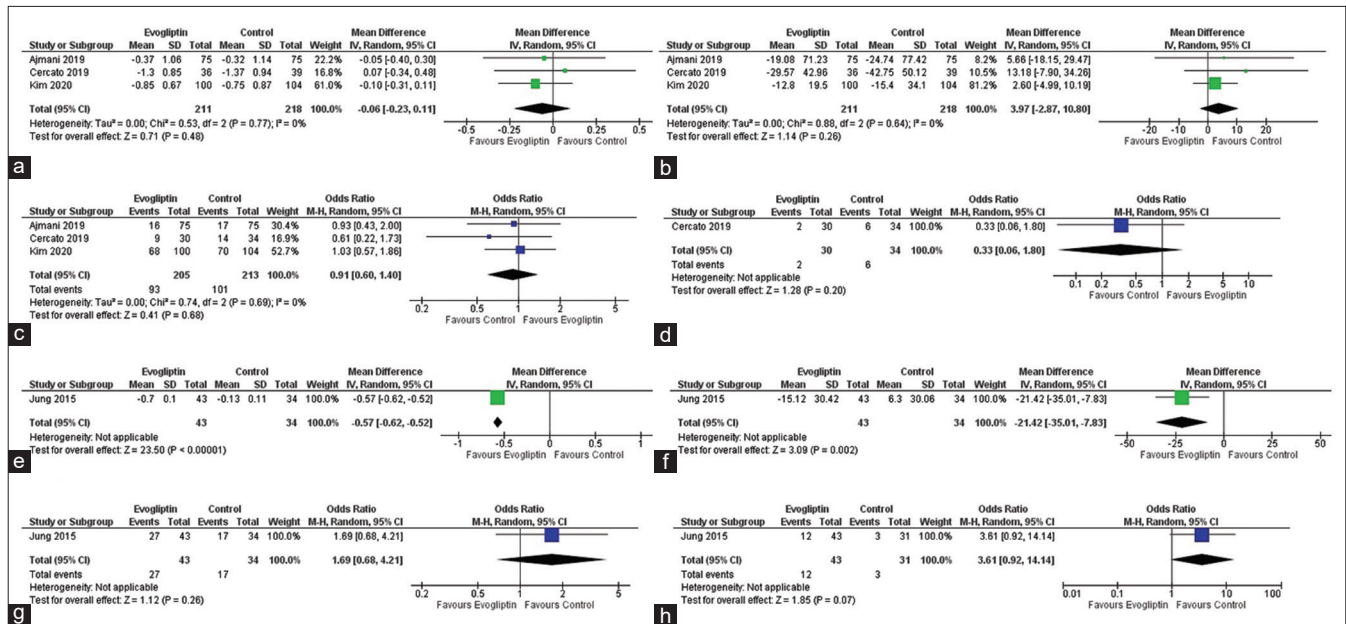


Figure 3: Forest plot highlighting the impact of evogliptin after 12 weeks of therapy on (a) HbA1c (as compared to ACG); (b) fasting glucose (as compared to ACG); (c) percent of people achieving HbA1c <7% (as compared to ACG); (d) percent of people achieving HbA1c <6.5% (as compared to ACG); (e) HbA1c (as compared to PCG); (f) fasting glucose (as compared to PCG); (g) HbA1c <7% (as compared to PCG); and (h): HbA1c less than 6.5% (as compared to PCG). ACG: active control group; PCG: passive control group

$P < 0.001$; Figure 3e; MCE] and 24 weeks [MD -0.28% (95% CI: -0.47 – -0.09%); $P = 0.004$; Figure 4e; HCE] follow-up.

Effect of evogliptin on secondary outcomes

Fasting plasma glucose

Four studies with 506 patients analyzed the impact of evogliptin on FPG at 12 weeks and 3 studies with 514 patients evaluated it at 24 weeks of follow-up. When compared to the ACG, evogliptin was noninferior to sitagliptin/linagliptin with regards to FPG reduction at 12 weeks [MD 3.97 mg/dL (95%

CI: -2.87 – 10.8 mg/dL); $P = 0.26$; $I^2 = 0\%$ (low heterogeneity); Figure 3b; HCE] and 24 weeks of follow-up [MD 0.53 mg/dL (95% CI: -5.52 – 6.58 mg/dL); $P = 0.86$; $I^2 = 0\%$ (low heterogeneity); Figure 4b; HCE].

Similar analysis was not possible for evogliptin compared to PCG as data was available only from one study at 12 weeks of follow-up (Jung *et al.*, 2015) and 24 weeks of follow-up (Park *et al.* 2017). Analysis of data from these studies revealed evogliptin was superior to placebo with

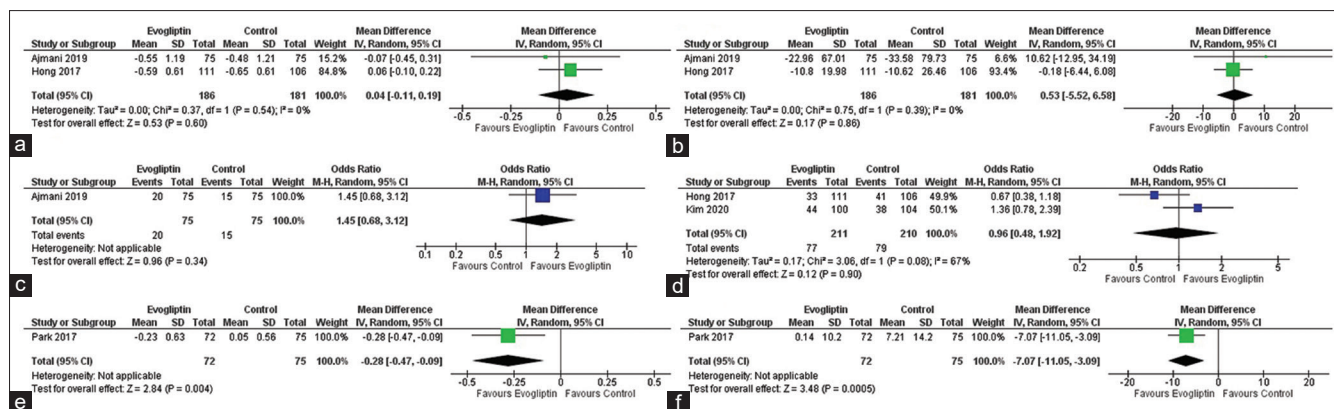


Figure 4: Forest plot highlighting the impact of evogliptin after 24 weeks of therapy on (a) HbA1c (as compared to ACG); (b) fasting glucose (as compared to ACG); (c) percent of people achieving HbA1c <7% (as compared to ACG); (d) percent of people achieving HbA1c <6.5% (as compared to ACG); (e): HbA1c (as compared to PCG); and (f): Fasting glucose (as compared to PCG) RCT: randomized controlled trial. ACG: active control group; PCG: passive control group

regards to FPG reduction at 12 weeks [MD -21.42 mg/dL (95% CI: -35.01 – 7.83 mg/dL); $P = 0.002$; Figure 3f; MCE] and 24 weeks [MD -7.07 mg/dL (95% CI: -11.05 – 3.09 mg/dL); $P = 0.0005$; Figure 4f; HCE] follow-up.

Glycated Haemoglobin <7%

Four studies with 495 patients and one study with 150 patients analyzed the impact of evogliptin on attaining glycemic target of HbA1c <7% at 12 weeks and 24 weeks of follow-up, respectively. When compared to the ACG, evogliptin was noninferior to sitagliptin/linagliptin with regards to percent of patients achieving HbA1c <7% at 12 weeks [Odds Ratio (OR) 0.91 (95% CI: 0.60–1.40); $P = 0.68$; $I^2 = 0\%$ (low heterogeneity); Figure 3c; HCE] and 24 weeks of follow-up [OR 1.45 (95% CI: 0.68–3.12); $P = 0.34$; Figure 4c; HCE].

Similar analysis was not possible for evogliptin compared to PCG as data was available only from one study at 12 weeks of follow-up (Jung *et al.*, 2015) and 24 weeks of follow-up (Park *et al.* 2017). Analysis of data from these studies revealed that percent of patients achieving HbA1c <7% at 12 weeks was higher in the evogliptin group as compared to those receiving placebo at 12 weeks follow-up [OR 1.69 (95% CI: 0.68–4.21); $P = 0.26$; Figure 3g; HCE], but statistically not significant. No similar data was available for the PCG at 24 weeks follow-up.

Glycated Haemoglobin <6.5%

Impact of evogliptin on percent of patient attaining glycemic target of HbA1c <6.5% at 12 weeks was assessed in two studies with 138 patients and that at 24 weeks was analyzed in another two studies with 421 patients. When compared to ACG, evogliptin was noninferior to sitagliptin/linagliptin with regards to percent of patients achieving HbA1c <6.5% at 12 weeks [OR 0.33 (95% CI: 0.06–1.80); $P = 0.20$; Figure 3e; MCE] and 24 weeks of follow-up [OR 0.96 (95% CI: 0.65–1.42); $P = 0.83$; $I^2 = 67\%$ (moderate heterogeneity); Figure 4e; MCE]. On analysis of data from PCG, percent of patients achieving HbA1c <6.5% at 12 weeks was higher in the evogliptin group as compared to placebo at 12 weeks

follow-up, which approached statistical significance [OR 3.61 (95% CI: 0.92–14.14); $P = 0.07$; Figure 3e; MCE]. However this data was available only from one study. No similar data was available for the PCS at 24 weeks follow-up.

Safety

Data from six studies (887 patients) was analyzed to evaluate the impact of evogliptin on the occurrence of adverse events [(total adverse events (TAEs) and severe adverse events (SAEs)]. The occurrence of TAEs was not statistically different in patients receiving evogliptin as compared to controls [RR 0.98 (95% CI: 0.72–1.32); $P = 0.89$; $I^2 = 17\%$ (low heterogeneity); Figure 5a; HCE]. The occurrence of SAEs was not statistically different in patients receiving evogliptin as compared to controls [RR 0.65 (95% CI: 0.25–1.67); $P = 0.37$; $I^2 = 0\%$ (low heterogeneity); Figure 5b; HCE]. There were no reports of pancreatitis in any of the study participants in all the six studies evaluated in this meta-analysis.

Data from five studies (801 patients) were analyzed to evaluate the risk of symptomatic and asymptomatic hypoglycemia in patients receiving evogliptin as compared to the controls. Patients receiving evogliptin did not have increased risks of symptomatic [RR 0.46 (95% CI: 0.10–2.16); $P = 0.32$; $I^2 = 0\%$ (low heterogeneity); Figure 5c; HCE] and asymptomatic [RR 1.09 (95% CI: 0.61–1.97); $P = 0.77$; $I^2 = 0\%$ (low heterogeneity); Figure 5d; HCE] hypoglycaemia.

Lipid parameters and insulin resistance

Data from two studies (421 patients) were analyzed to evaluate the impact of evogliptin on different lipid parameters (total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)). No significant difference was noted among patients receiving evogliptin as compared to controls with regards to total cholesterol [MD -0.93 mg/dL (95% CI: -5.73 – 3.87 mg/dL); $P = 0.71$; $I^2 = 0\%$ (low heterogeneity)], triglycerides [MD -3.09 mg/dL (95% CI: -17.79–11.61 mg/dL); $P = 0.68$; $I^2 = 0\%$ (low heterogeneity)], LDL-C [MD -1.37

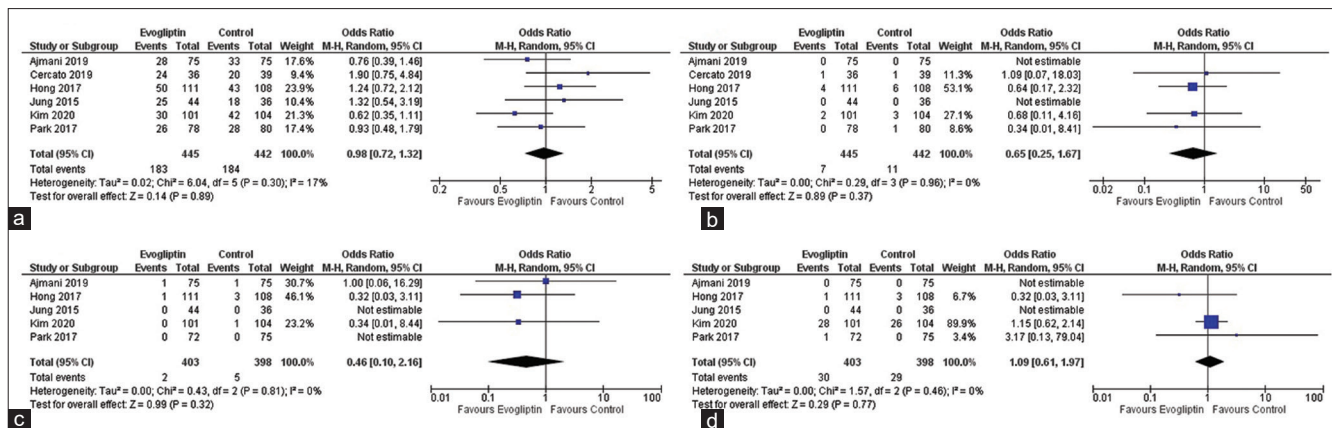


Figure 5: Forest plot highlighting the side effect profile of the use of evogliptin as compared to controls focusing on (a): Total Adverse Events (TAEs); (b): severe Adverse Events (SAEs); (c): symptomatic hypoglycaemia; and (d): asymptomatic hypoglycaemia

mg/dL (95% CI: -5.92–3.18 mg/dL); $P = 0.56$; $I^2 = 0\%$ (low heterogeneity)] and HDL-C [MD -0.36 mg/dL (95% CI: -1.90–1.18 mg/dL); $P = 0.65$; $I^2 = 0\%$ (low heterogeneity)].

Data from two studies (290 patients) were analyzed to evaluate the impact of evogliptin on measures of insulin resistance. There was no significant difference in HOMA-IR [MD -0.01 (95% CI: -0.73–0.72); $P = 0.99$; $I^2 = 0\%$ (low heterogeneity)] and QUICKI [MD 0.00 (95% CI: -0.00–0.00); $P = 0.96$; $I^2 = 0\%$ (low heterogeneity)] among patients receiving evogliptin as compared to controls.

Funnel plot of all the included studies in the meta-analysis (assessing the publication bias) of the main outcomes assessed in this study. High publication bias was evident for HbA1c (12 weeks) and fasting glucose (12 weeks) for PCG. With regards to all the other parameters, there was no evidence of publication bias as all the studies fell well within the funnel plot. The SoF of the key parameters of this meta-analysis has been elaborated in Table 2.

DISCUSSION

No other class of antidiabetes medications has such a multitude of molecules as the DPP4i with 12 different DPP4i approved for clinical use in different countries across the globe.^[5] DPP4i gained much popularity after the launch of sitagliptin in 2006, because of the ease of their use, tolerability, good safety profile, and low hypo glycaemic potential.^[19] Evogliptin belongs to the newer generation of DPP4i.^[5] With some special properties such as the high specificity for the DPP4 enzyme, a long half-life facilitating a once daily dosage, dual renal, and hepatic excretion permitting its use in mild to moderate renal failure as well as hepatic disease.^[5,19] This meta-analysis highlights the good glycaemic efficacy of evogliptin in comparison to other established DPP4i like sitagliptin and linagliptin over period of 12–24 weeks. Evogliptin was noninferior to sitagliptin and linagliptin but superior to placebo with regards to achieving good glycaemic control, as reflected in HbA1c and FPG reduction. This meta-analysis provides reassuring data on the

safety of evogliptin. It is well tolerated and as compared to other DPP4i and placebo, without increased risk of adverse events. It was found to be lipid neutral and had no significant impact on insulin resistance parameters (HOMA-IR and QUICKI).

We must highlight that data with regards to evogliptin use from RCT is largely restricted to 24 weeks. Hence, there remains the need for RCTs with longer follow-up to establish the glycaemic durability of evogliptin. These RCTs would also help us in generating useful long-term cardiovascular and renal safety data of evogliptin. In animal studies, evogliptin has been demonstrated to reduce the high-fat diet-induced atherosclerotic plaque area in the ApoE knockout mouse model.^[20] The protective effect of evogliptin on atherosclerotic progression is believed to be through inhibition of vascular inflammation.^[20]

DPP4 inhibitors have demonstrated protective effects against diabetic kidney disease, with encouraging data coming from linagliptin and sitagliptin.^[21] In animal models, evogliptin has been observed to have beneficial impact on renal fibrosis through inhibition of the transforming growth factor- β /Smad3 signaling pathway.^[22] It would be interesting to know the impact of evogliptin on urine albumin excretion. Evogliptin has been found to significantly reduce hepatic triglyceride accumulation, inflammation, and fibrosis as well as restored insulin sensitivity, in mice models of hepatic steatosis and steatohepatitis induced through high fat high fructose diet.^[23] Although from mechanistic studies, evogliptin is largely “nephro-safe” and “hepatic-safe,” we need focused RCTs in special populations (viz. people living with chronic kidney disease, liver disease), before evogliptin use can be recommended in these special clinical scenarios.

To conclude, it may be said that this first meta-analysis on the efficacy and safety of evogliptin in T2DM provides us with reassuring data on the good glycaemic efficacy with good tolerability of this molecule over a period of 6 months clinical use.

Table 2: Summary of findings

Evogliptin vs. Controls in the management of type-2 diabetes						
Patient or population: people living with type-2 diabetes Setting: Randomized controlled trial having either active control subgroup (sitagliptin/imagliptin) or passive control subgroup (placebo) Intervention: Evogliptin 5 mg/d Comparison: Controls						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Evogliptin 5 mg/d	Risk with Controls				
HbA1c (12 weeks)-Active Control Group	The mean HbA1c (12 weeks)-Active Control Sub-group was 7.87%	MD 0.06% lower (0.23 lower to 0.11 higher)	-	429 (3 RCTs)	⊕⊕⊕○ MODERATE ^b	
HbA1c (12 weeks)-Passive/Placebo Control Group	The mean HbA1c (12 weeks)-Passive/Placebo Control Subgroup was 7.32%	MD 0.57% lower (0.62 lower to 0.52 lower)	-	77 (1 RCT)	⊕⊕⊕○ MODERATE	
HbA1c (24 weeks)-Active Control Group	The mean HbA1c (24 weeks)-Active Control Sub-group was 7.87%	MD 0.04% higher (0.11 lower to 0.19 higher)	-	367 (2 RCTs)	⊕⊕⊕⊕ HIGH	
HbA1c (24 weeks)-Passive/Placebo Control Group	The mean HbA1c (24 weeks)-Passive/Placebo Control Subgroup was 7.32%	MD 0.28% lower (0.47 lower to 0.09 lower)	-	147 (1 RCT)	⊕⊕⊕⊕ HIGH	
Fasting Glucose (12 weeks)-Active Control Group	The mean fasting Glucose (12 weeks)-Active Control Sub-group was 167.87 mg/dL	MD 3.97 mg/dL higher (2.87 lower to 10.8 higher)	-	429 (3 RCTs)	⊕⊕⊕⊕ HIGH	
Fasting Glucose (12 weeks)-Passive/Placebo Control Group	The mean fasting Glucose (12 weeks)-Passive/Placebo Control Sub-group was 146.7 mg/dL	MD 21.42 mg/dL lower (35.01 lower to 7.83 lower)	-	77 (1 RCT)	⊕⊕⊕○ MODERATE ^a	
Fasting Glucose (24 weeks)-Active Control Group	The mean fasting Glucose (24 weeks)-Active Control Sub-group was 167.87 mg/dL	MD 0.53 mg/dL higher (5.52 lower to 6.58 higher)	-	367 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Fasting Glucose (24 weeks)-Passive/Placebo Control Group	The mean fasting Glucose (24 weeks)-Passive/Placebo Control Subgroup was 146.7 mg/dL	MD 7.07 mg/dL lower (11.05 lower to 3.09 lower)	-	147 (1 RCT)	⊕⊕⊕⊕ HIGH	
Total adverse events (number of people)	416 per 1,000	409 per 1,000 (345 to 475)	OR 0.97 (0.74-1.27)	887 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Severe adverse events (number of people)	25 per 1,000	16 per 1,000 (6 to 40)	OR 0.65 (0.25-1.64)	887 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Symptomatic hypoglycaemia	13 per 1,000	6 per 1,000 (1 to 25)	OR 0.45 (0.10-2.01)	801 (5 RCTs)	⊕⊕⊕⊕ HIGH	
Asymptomatic hypoglycaemia	73 per 1,000	78 per 1,000 (46 to 132)	OR 1.08 (0.61-1.93)	801 (5 RCTs)	⊕⊕⊕⊕ HIGH	
HbA1c <7% (12 weeks)-Active Control Group	474 per 1,000	451 per 1,000 (351 to 558)	OR 0.91 (0.60-1.40)	418 (3 RCTs)	⊕⊕⊕⊕ HIGH	
HbA1c <7% (12 weeks)-Passive/Placebo Control Group	500 per 1,000	628 per 1,000 (405 to 808)	OR 1.69 (0.68-4.21)	77 (1 RCT)	⊕⊕⊕⊕ HIGH	
HbA1c <7% (24 weeks)-Active Control Group	200 per 1,000	266 per 1,000 (145 to 438)	OR 1.45 (0.68-3.12)	150 (1 RCT)	⊕⊕⊕⊕ HIGH	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; OR: Odds ratio. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. The single study here lies outside the Funnel plot suggestive of presence of significant publication bias (Supplementary Figure 2). bFunnel plot is suggestive of the presence of most of the studies outside the plot; hence, it is likely that significant publication bias is present (Supplementary Figure 2)

Authors' contribution

Study was planned by DD and MS. Literature search and review was done by LKS and SB. Data extraction was done by SB and AK. Data analysis was done by DD. All authors contributed equally to the manuscript preparation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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RISK OF BIAS ASSESSMENT FOR THE METANALYSIS

Ajmani 2012	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Randomized Controlled Trial (RCT)
Allocation Concealment (Selection Bias)	Low Risk	Permuted block randomization method used
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Double blinded study, participants and personal were blinded
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blinded study, participants and personal were blinded
Incomplete Outcome Data (Attrition Bias)	Low Risk	184 patients were randomized in this study; 92 patients each in the evogliptin 5mg/d and sitagliptin 100 mg/d arms; data from 150 patients were analyzed at the end of the study (75 patients in each arms); hence attrition rate was 18.47%. An attrition rate of less than 20% was considered to be low
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	The study was sponsored by Alkem Laboratories India. The corresponding author was Deputy General Manager-Medical, Alkem Laboratories Ltd, Mumbai India
Cercato 2019	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Double-blind, double-dummy, parallel group RCT of 12 weeks duration
Allocation Concealment (Selection Bias)	Low Risk	Randomization method was block randomization
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Double dummy parallel group RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double dummy parallel group RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	From the 146 randomized subjects, 126 (86.3%) completed the study.
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This study was sponsored by Eurofarma Laboratórios S.A., which provided funding for all study procedures, study treatment, and investigators fees.
Kim 2020	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	This trial consisted of the following three periods: a 2-week, single-blind, run-in period; a 12-week, double-blind, randomized (analyzed in this meta-analysis), treatment period; and a 12-week, open-label, extension Period
Allocation Concealment (Selection Bias)	Unclear risk	Randomization method not available in the manuscript
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	102 and 105 patients were randomized to the evogliptin group and the linagliptin group, of which 96 (94%) patients in the evogliptin group and 98 (93%) patients in the linagliptin group completed the 12-week main study
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	Low Risk	This study was funded by Dong-A ST, Co., Ltd., Seoul, Republic of Korea. The funding source had no role in the study design, data collection, data analysis, decision to publish, or preparation of the manuscript.
Park 2017	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Double blinded randomized controlled trial (RCT) of 24 week duration
Allocation Concealment (Selection Bias)	Unclear Risk	Method of randomization not clear
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blinded RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	From the initially randomised 160 patients (80 in each group); data from 147 patients (91.87%) (72 patients in the evogliptin group and 75 patients in the placebo group) completed the 24-week treatment
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	The 14 th author is from division of Biostatistics, Clinical Development Team, Dong-A ST Co., LTD., Seoul, Korea, the pharmaceutical company associated with the development of this molecule for the Korean market

Ajmani 2012	Risk of Bias	Author Judgement
Jung 2015	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Double blinded placebo controlled RCT of 12 weeks duration
Allocation Concealment (Selection Bias)	Low Risk	Block randomization done; randomization schedule generated using SAS System 9.2 (SAS Institute, Cary, NC, USA).
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blinded RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	From the 158 patients randomized, data from 153 patients were analyzed (96.83%)
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	The 11 th author was from the Clinical Development Team, Dona-A ST, Seoul, Republic of Korea. This study was supported by Dong-A ST Co., Ltd Seoul, Republic of Korea. The sponsor participated in the study design, data collection and analysis of the data, but had no role in the writing of the manuscript or in the decision to submit the manuscript for publication.
Hong 2017	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Double blinded active control RCT of 24 weeks duration
Allocation Concealment (Selection Bias)	Low Risk	Double blind active control RCT; Block randomization
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blinded RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	From the initially randomized 222 patients, data from 205 patients (92.34%) were analyzed after 24 weeks follow up
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	One of the authors Dong-Min Hwang was an employee of Dong-A ST Co., Ltd pharmaceuticals involved in the development of this molecule for the market. He was involved in data analysis