REVIEW

Systematic review and meta-analysis of teneligliptin for treatment of type 2 diabetes

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Abstract

Background and aim There are efficacy and safety concerns related to teneligliptin treatment. A systematic review of randomized controlled trials (RCTs) was undertaken to comprehensively profile the efficacy and safety of teneligliptin in the treatment of type 2 diabetes mellitus (T2DM).

Methods Thirteen studies were chosen from a search of scientific databases for RCTs using teneligliptin as a monotherapy or as an adjunct to other glycemic agents with pre-specified inclusion criteria. We calculated weighted mean differences (WMDs) and 95% confidence intervals (CIs) in each included trial and pooled the data using a random-effects model.

Results Thirteen studies enrolled 2853 patients were identified. Teneligliptin treatment was associated with weight gain (vs. placebo, weighted mean difference (WMD) 0.28 kg; 95% CI -0.20–0.77 kg; $I^2 = 86\%$; $P = 0.25$). Compared to monotherapy, add on therapy with teneligliptin showed significant improvement in FPG mg/dl levels (WMD -16.75 mg/dl; 95% CI -19.38 to -14.13 mg/dl), HOMA-β (WMD 7.91; 95% CI 5.38–10.45) and HOMA-IR (WMD -0.27; 95% CI -0.46 to -0.07). The improvement in HbA1c was greater with monotherapy (WMD -8.88 mmol/mol; 95% CI -9.59 to -8.08 mmol/mol). There was no significant risk of any hypoglycemia with teneligliptin compared to placebo (OR 0.84; 95% CI 0.44–1.60; $I^2 = 0\%$; $P = 0.60$). However, the risk was 1.84 times high when combined with other glycemic agents. The risk of cardiovascular events was comparable, regardless of treatment duration when compared to placebo or any other active comparator (OR 0.79; 95% CI 0.40–1.57; $I^2 = 0\%$; $P = 0.50$). [PROSPERO, CRD42022360785].

Conclusions Teneligliptin is an effective and safe therapeutic option for patients with T2DM, both as monotherapy and as add-on therapy. However, additional large-scale, high-quality, long-term follow-up clinical trials with diverse ethnic populations are required to confirm its long-term efficacy and safety.

Keywords Teneligliptin · Glycemic efficacy · Safety · Meta-analysis · Type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease and its mortality and morbidities are rising at alarming rates [1]. Dipeptidyl peptidase-4 (DPP-4) inhibitors (formally known as gliptins) belong to the class of incretin mimetics [2]. These medications have been available for the treatment of T2DM over a decade ago [3]. DPP-4 enzyme is widely distributed throughout the body [4] and it rapidly inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) [5] and, thus the incretins simulate the pancreatic beta cells to produce insulin [6, 7]. While, some anti-inflammatory agents fail to preserve beta cells [8]. Hence, inhibitors of DPP-4 enzyme provide a strategic option for management of T2DM [9–11] with promising reduction of HbA$_{1c}$

in Asians than non-Asians [12]. In general, incretins improve pancreatic beta cell function [13]. Patients with T2DM have a 60% reduction in beta cell function when compared to nondiabetics [14]. The decreased beta cell mass of 50–60% is not enough to cause diabetes every time [15].

Teneligliptin is a gliptin, but it is structurally distinct from other gliptins, comprising J-shaped structure with an anchor lock domain. Consequently, it has high receptor affinity leading to a longer duration of action, maintaining a consistent glucose levels throughout the day. The pleiotropic effects of teneligliptin on vascular function, lipids, and possibly obesity may be advantageous for diabetics who are obese and those at high risk for diabetic vascular complications [16]. Teneligliptin was developed in Japan, is now approved and available for the treatment of T2DM in Japan, Korea, India, and Argentina. There are currently eight gliptins available in the market (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin, gemigliptin, evogliptin and teneligliptin) [17] and adequate number of clinical trials have been conducted around the world to determine its safety and efficacy besides teneligliptin. Few studies have been conducted on teneligliptin, and the pooled randomised clinical trial data are still insufficiently powered to detect the beneficial or detrimental effect with teneligliptin. Therefore, evidence on its safety and efficacy as monotherapy and add-on therapy with teneligliptin should be updated.

Methods

The present review was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) extension statement for reporting systematic reviews that included network meta-analysis of health care interventions [18]. The present meta-analysis was registered with International prospective register of systematic reviews, Centre for Reviews and Dissemination (PROSPERO), CRD42022360785.

Search strategy

A systematic review of the literature was done using the databases PubMed, Cochrane, Scopus, and Embase, as well as https://www.clinicaltrials.gov, from inception to September 30th 2022. The search strategy for our chosen study was performed in accordance with the PRISMA statement. The following MeSH terms were employed in a Boolean query which combined each of the separately searched. The key terms were DPP-4i (OR) "Teneligliptin," "MP-513," "T2DM," and "Type 2 diabetes mellitus" to search data and these terms were modified to comply with the relevant rules in each database. We also searched the data using ("Diabetes Mellitus, Type 2"[MeSh] AND teneligliptin"). Furthermore, we sought for

teneligliptin with other antidiabetic drugs (AND) in combination of teneligliptin. No restriction of language or publication date was applied. We analysed full-text articles, entered search results into a citation management programme, screened titles, and abstracts to avoid duplication. Duplicates of those that were meeting our review criteria were excluded. Three authors screened for duplication and the fourth author resolved the disagreements of consensus.

Study selection

The studies were chosen based on an initial screening of identified titles and abstracts, followed by a second screening for full-text articles. The eligible studies were considered if they met the following PICOS criteria., with the patients (P) being people living with T2DM; the intervention (I) being the use of teneligliptin with any dose for managing T2DM not less than 12 weeks; the control (C) being patients either on placebo or other active anti-diabetic agents; and the outcome (O) of interest was the impact on body weight, fasting plasma glucose (FPG), homeostasis model assessment of beta cell function (HOMA-β), homeostasis model assessment of insulin resistance (HOMA-IR), glycated hemoglobin (HbA$_{1c}$ %) from baseline to end of the treatment including the follow-up. The incidence of adverse events (AEs) of hypoglycemia, cardiovascular events and deaths were assessed. The study designs (S) being of RCTs were included in this meta-analysis. Different search engines were used to find and retrieve the studies with RCTs of safety and effectiveness of teneligliptin. The conference reports and abstracts were not archived due to insufficient information.

Data extraction

Three independent reviewers (RK. P., J. Ch, and VR. N) carefully extracted the abstract in accordance with the inclusion criteria. Any disagreements were resolved by the senior reviewers (S.K and S.M) until agreement was reached on all issues. A standard data extraction format was used to collect the information retrieved from the RCTs which included, the name of the first author, year of publication, country, inclusion criteria, follow-up study, background treatments, comparator, mean age of population, total number of patients, percentage of male/female, total participants, total number of hypoglycemic events, mean values of HOMA-β, mean of HOMA-IR, and mean HbA$_{1c}$ %.

Study population

Inclusion criteria

In our review, we included randomised controlled trials (RCTs) of teneligliptin as monotherapy or in combination

with any anti-diabetic agents in patients with T2DM for at least 12 weeks (any number of arms) in comparison with placebo. Inclusion of studies with teneligliptin for the treatment of T2DM according to WHO diagnostic criteria were as follows: (1) patients, of any ethnicity and age 18 years or older of either gender with $HbA_{1c} \geq 6.5\%$ (2) Intervention, use of any dose of teneligliptin as monotherapy or add on to any other anti-diabetic agents with duration not less than 12 weeks. (3) Comparison, placebo, or active comparators with or without background therapy. (4) Outcomes: at least one of the following parameters was reported: (a) body weight, (b) FPG, (c) HOMA-β, (d) HOMA-IR and (e) HbA_{1c} %. (5) The incidence of hypoglycemia, cardiovascular events such as hospitalisation for heart failure, stroke, QT prolongation, and death were also evaluated as safety parameters in this review.

Exclusion of criteria

Studies were excluded, if they included patients of type-1 diabetes (T1DM), $HbA_{1c} > 10\%$, history of renal, hepatic failures, pancreatitis, and cardiovascular disorders.

Risk of bias assessment

Three authors independently evaluated the risk of bias for all included RCTs. Bias including selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias, such as design-specific risks of bias, baseline imbalance, blocked randomization in unblinded trials, were assessed with the Cochrane Risk of Bias tool. Any discrepancies were resolved by discussion. The overall risk of bias for each study was provided (Supplementary Material Figs. 1and2).

Statistical analysis

All analyses were carried out using Review Manager version 5.3.1; formally known as *Cochrane's Review Manager*. The continuous outcomes were computed to weighted mean differences (WMDs) using Der-Simonian and Laird random-effects methods. We used Mantel–Haenszel fixed-effects methods to calculate odds ratios (ORs) for dichotomous outcomes, with a treatment arm continuity correction and zero total events trials included when necessary [19]. Heterogeneity was quantified using the I^2 statistic, with the values ranging from 0% to 100% and values of 25%, 50% and 75% representing low, moderate, and high levels of heterogeneity, respectively. In general, 50% of I^2 value represented substantial heterogeneity [20]. The safety and efficacy of teneligliptin's meta-analysis was performed between monotherapy (teneligliptin or placebo) and add-on therapy, i.e., other anti-diabetic agents with teneligliptin or placebo).

Furthermore, sub-group analysis was employed to assess the results with high heterogeneity ($I^2 \geq 75\%$). The studies of sub-groups were stratified based on the duration of treatment with teneligliptin < 16 weeks [22, 24, 25, 27] and > 16 weeks [21, 23, 26, 28–33].

Results

Literature search and study inclusion

The PRISMA flow diagram summarises the study selection process (Supplementary Material Fig. 3). The electronic search retrieved 318 potentially relevant records, of which 133 duplicates records were removed. After screening the title and abstract for inclusion/exclusion criteria, 104 of the 188 records were excluded. The eligibility of the remaining 84 full-text articles was determined. The remaining 71 articles were excluded for various reasons, including: trial duration of 4 weeks ($n = 7$), incongruent for study ($n = 12$), non-eligible comparisons ($n = 15$), non-randomized ($n = 6$), and narrative or systematic reviews ($n = 31$). Finally, 13 RCTs fulfilled the inclusion criteria and were considered for the proposed study. The included studies comprise of 2853 patients, of which five studies were Monotherapy [21–25] and eight studies [26–33] were add-on therapy with Teneligliptin or Placebo. In the included studies, the effect of teneligliptin on glycemic parameters, change of body weight, and adverse events, such as hypoglycemia, cardiovascular events, and mortality were evaluated. All these studies were randomized controlled trials (RCT) of teneligliptin on patients with T2DM. The characteristics of the included studies in this meta-analysis were represented in Supplementary Material Table 1.

Efficacy parameters

Change of body weight

A total of eight studies were evaluated for change of body weight, which comprised two of monotherapy [21, 23] and six add-on therapy [26, 28, 29, 31–33] studies, with a total of 1422 subjects. Treatment with teneligliptin monotherapy resulted in increase of body weight compared with placebo (Weighted mean difference WMD, 0.60 kg; (95% CI − 0.19 to 1.39 kg; $I^2 = 72\%$). A marginal increase in body weight of 0.17 kg was observed in add-on therapy group. The overall effect of teneligliptin on body weight was not statistically significant (WMD 0.28 kg; 95% CI − 0.20 to 0.77; $I^2 = 86\%$; $P = 0.25$). Teneligliptin with canagliflozin showed negligible reduction on body weight (WMD − 0.81 kg) (Supplementary Material Fig. 4). In contrast to sub-group analysis, the included study's treatment duration was more than 16 weeks.

Hence, it was not possible to perform sub-group analysis (Supplementary Material Fig. A).
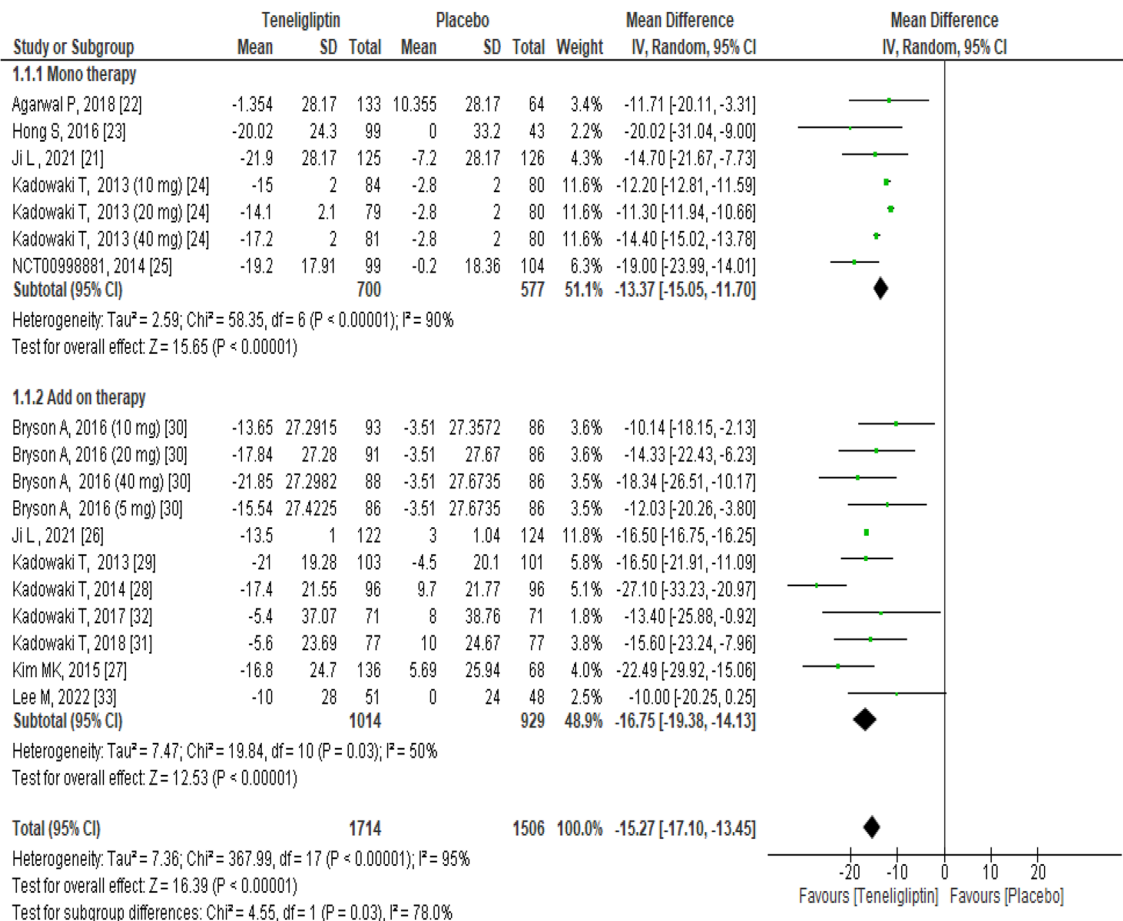
Effect on fasting plasma glucose (mg/dl)

Data from thirteen studies involving 3220 people with T2DM were analysed to identify the impact of teneligliptin treatment as both mono and add-on therapy on FPG levels [21–33]. Owing to comparison, monotherapy (WMD − 13.37 mg/dl; 95% CI − 15.05 to − 11.70; $I^2=90\%$) was non-inferior in reducing FPG compared to add-on therapy (WMD − 16.75 mg/dl; 95% CI − 19.38 to − 14.13; $I^2=50$) ($P<0.00001$). The overall effect of teneligliptin has reduced FPG levels by − 15.27 mg/dl compared to placebo (WMD − 15.27 mg/dl; 95% CI − 17.10 to − 13.45; $I^2=95\%$) ($P<0.00001$) and the difference between the groups were statistically significant in reducing FPG ($P=0.03$ and $I^2=78\%$). The substantial WMD was noticed with glimepiride adding to teneligliptin [28], which showed greatest reduction of FPG − 27.10 mg/dl (95% CI − 33.23 to 20.97) (Fig. 1). In sub-group analysis, the effect of teneligliptin

with more than 16 weeks of treatment has better reduction of FPG, WMD was − 16.64 mg/dl (WMD − 16.64 mg/dl; 95% CI − 19 to − 14.28 mg/dl; $I^2=39\%$) compared to less than 16 weeks of treatment, WMD was − 13.62 mg/dl (WMD − 13.62 mg/dl; 95% CI − 15.40 to − 11.85 mg/dl; $I^2=92\%$). The test for sub-group differences was significant ($P=0.05$ and $I^2=75.1\%$) (Supplementary Material Fig. B).

HbA$_{1c}$ (%)

Thirteen studies [21–33] were reviewed for the reduction of glycated haemoglobin percentage, of which, five were of teneligliptin monotherapy [21–25] and eight [26–33] were add-on therapy. In pooled analysis, the WMD was − 0.68 (WMD − 0.68%; 95% CI − 0.85 to − 0.50; $I^2=100\%$; $P<0.00001$) and, in sub group analysis, monotherapy had greatest reduction of HbA$_{1c}$ WMD − 0.88% (95% CI − 0.95 to − 0.80; $I^2=89\%$; $P<0.0001$) compared to add-on therapy WMD − 0.62% (95% CI − 0.87 to − 0.37; $I^2=100\%$; $P<0.0001$) (Fig. 2). Of note, teneligliptin 40 mg/day as monotherapy (WMD − 1.00%) [24] exhibited highest

Fig. 1 Weighted mean difference in change from baseline in fasting plasma glucose (mg/dl): teneligliptin versus placebo or active comparators. Results are from inverse variance random-effects meta-analysis

improvement in HbA_{1c} (%), compared to teneligliptin 40 mg/day plus metformin (WMD − 0.63%) [30]. However, teneligliptin 20 mg/day with glimepiride (WMD − 1.00%) [28] had shown equivalent efficacy compared to teneligliptin 40 mg/day [24]. In subgroup analysis, there was no significant difference between duration of treatment and change in HbA_{1c} (%) ($P=0.07$ and $I^2=70.6\%$) (Supplementary Material Fig. C).

Safety outcomes
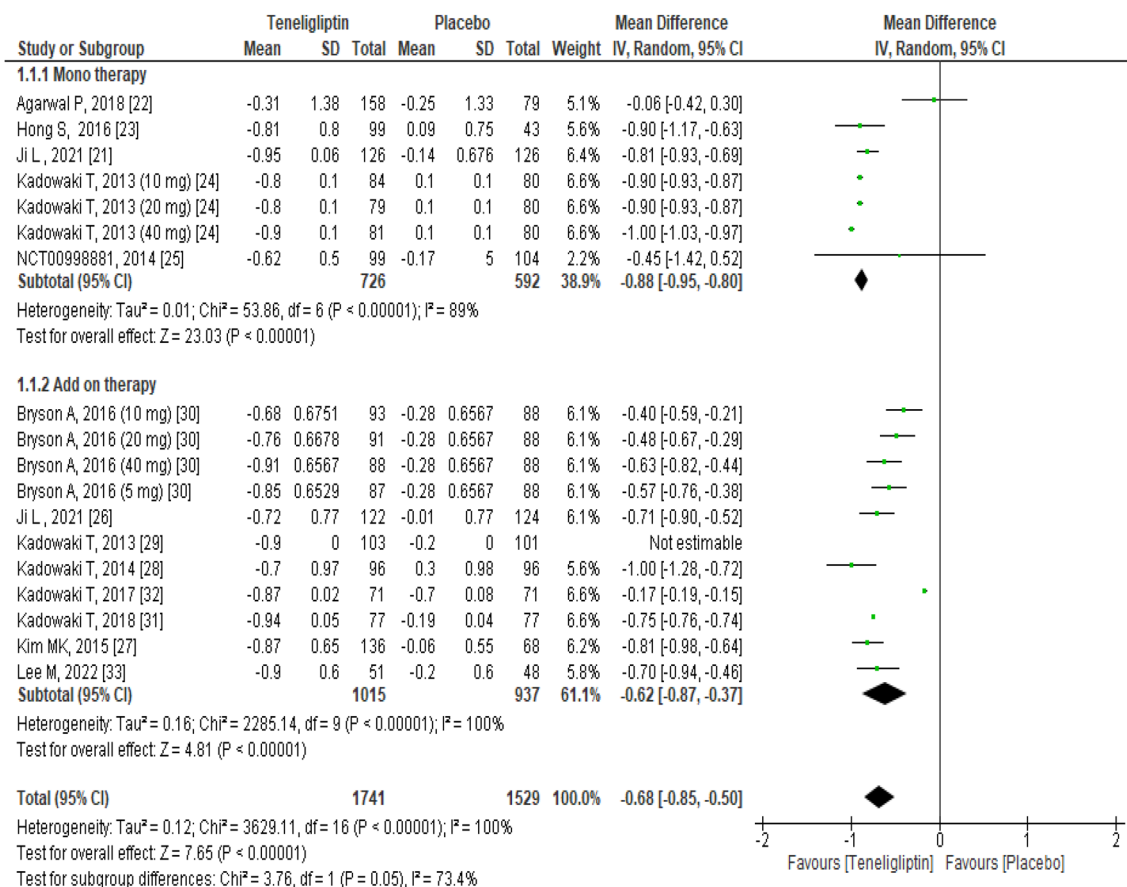
Risk of hypoglycemia

The current meta-analysis found no significant hypoglycemic incidence among the studies (mono and add-on therapy), and the incidence of hypoglycemia was similar in patients receiving teneligliptin versus placebo in monotherapy (OR 0.84; 95% CI 0.44–1.60; $I^2=0\%$; $P=0.60$). Of note, the odds of hypoglycemia were 1.84 times in add-on therapy (OR 1.84; 95% CI 1.03–3.27; $I^2=17\%$; $P=0.04$) compared to placebo. The overall risk of hypoglycemia was not statistically significant when compared to monotherapy and

add-on therapy ($P=0.21$) (Fig. 3). The odds of hypoglycemia were not significant in contrast to duration of treatment in sub-group analysis ($P=0.17$, $I^2=47.8\%$) (Supplementary Material Fig. F). However, the risk of hypoglycemia was predominantly high in teneligliptin with metformin [27, 30] and insulin [32].

Cardiovascular outcomes

Incidence of cardiovascular risk (CV) was similar in patients receiving teneligliptin compared to those receiving either placebo or any active comparator (OR 0.79; 95% CI 0.40–1.57; $I^2=0\%$; $P=0.50$) (Fig. 4). The odds of CV risk were also similar in sub-group analysis and the sub-group difference is not statistically significant ($P=0.38$, $I^2=0\%$) with duration of treatment (Supplementary Material Fig. G). Overall, fifteen CV events were observed in the monotherapy group, of which, five were in the teneligliptin-treated group and ten were in the placebo-treated group. Among them, one incidence of QT prolongation was noticed in teneligliptin-treated group [21]. Treatment emergent CV adverse events (stroke and other CV events) were chiefly

Fig. 2 Weighted mean difference in change from baseline in HbA_{1c} (%): teneligliptin versus active comparators. Results are from inverse variance random-effects meta-analysis

Study or Subgroup	Teneligliptin Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Monotherapy							
Agarwal P, 2018 [22]	6	158	1	79	3.3%	3.08 [0.36, 26.03]	
Hong S, 2016 [23]	0	99	1	43	5.4%	0.14 [0.01, 3.57]	
Ji L , 2021 [21]	8	127	7	127	17.1%	1.15 [0.41, 3.28]	
Kadowaki T, 2013, (10 mg) [24]	0	84	3	80	9.3%	0.13 [0.01, 2.58]	
Kadowaki T, 2013, (20 mg) [24]	1	79	3	80	7.7%	0.33 [0.03, 3.23]	
Kadowaki T, 2013, (40 mg) [24]	3	81	3	80	7.6%	0.99 [0.19, 5.04]	
NCT00998881, 2014 [25]	1	99	1	104	2.5%	1.05 [0.06, 17.04]	
Subtotal (95% CI)		727		593	52.9%	0.84 [0.44, 1.60]	
Total events	19		19				
Heterogeneity: Chi² = 5.14, df = 6 (P = 0.53); I² = 0%							
Test for overall effect: Z = 0.52 (P = 0.60)							
1.1.2 Add-on therapy							
Bryson A, 2016 (10 mg) [30]	5	93	0	80	1.3%	10.01 [0.54, 183.81]	
Bryson A, 2016 (20 mg) [30]	5	88	0	80	1.3%	10.60 [0.58, 194.90]	
Bryson A, 2016 (40 mg) [30]	2	88	0	80	1.3%	4.65 [0.22, 98.40]	
Bryson A, 2016 (5 mg) [30]	5	91	0	80	1.3%	10.24 [0.56, 188.09]	
Ji L , 2021 [26]	2	122	3	124	7.6%	0.67 [0.11, 4.09]	
Kadowaki T, 2013 [29]	0	103	0	101		Not estimable	
Kadowaki T, 2014 [28]	2	96	3	96	7.7%	0.66 [0.11, 4.04]	
Kadowaki T, 2017 [32]	9	77	5	71	12.0%	1.75 [0.56, 5.49]	
Kadowaki T, 2018 [31]	0	77	0	77		Not estimable	
Kim MK, 2015 [27]	4	136	2	68	6.7%	1.00 [0.18, 5.60]	
Lee M, 2022 [33]	1	51	3	48	7.9%	0.30 [0.03, 2.99]	
Subtotal (95% CI)		1022		905	47.1%	1.84 [1.03, 3.27]	
Total events	35		16				
Heterogeneity: Chi² = 9.68, df = 8 (P = 0.29); I² = 17%							
Test for overall effect: Z = 2.06 (P = 0.04)							
Total (95% CI)		1749		1498	100.0%	1.31 [0.86, 2.00]	
Total events	54		35				
Heterogeneity: Chi² = 15.77, df = 15 (P = 0.40); I² = 5%							
Test for overall effect: Z = 1.26 (P = 0.21)							
Test for subgroup differences: Chi² = 3.12, df = 1 (P = 0.08), I² = 67.9%							

Fig. 3 Odds ratio for incidence of hypoglycemia: results are from Mantel–Haenszel fixed effects meta-analysis with a treatment arm continuity correction

observed in add on therapy group compared to placebo [26, 30, 31]. No death was reported among patients who were treated with teneligliptin, and one death was reported in placebo group ($N = 80$) [24] of monotherapy (Supplementary Material Table 2).

Discussion

The study examined the effect of teneligliptin on glycemic parameters and body weight. The findings revealed that teneligliptin was effective in reduction of FPG, HOMA-IR, HbA1c and improvement of beta call function (HOMA-β), both as mono therapy and add on therapy. However, teneligliptin was associated with a slight increase in body weight compared to placebo or other active comparators. Risk for hypoglycemia was similar to placebo and lower than with other active comparators. In addition, results for incidence of certain cardiovascular events (QT prolongation, angina pectoris, stroke palpitations etc.) and all-cause mortality were reassuring. In this review we found a high level of heterogeneity (I^2, 75–100%) despite performing sub group analysis, However, heterogeneity of sub-group differences

was minimally reduced. We believe that, high I^2 values are because of, most of the populations being Asians and are positively responding to incretins [34] due to variations in gene and lifestyle [35].

The efficacy and safety of teneligliptin examined in earlier systematic review were with limited studies [36] which included treatment with less than 4-week duration, and with inadequate data on cardiovascular and total mortality. Furthermore, the current evidence on teneligliptin needed to be updated. Hence, we attempted to review the most recent and comprehensive summary of the available evidence regarding teneligliptin as of September 2022. We employed an exhaustive search and performed sensitivity analysis to ensure the robustness and validity of our results. Treatment with teneligliptin resulted in slight increase of body weight (0.28 kg) compared to placebo. Notably, comparison with monotherapy (0.60 kg), add on therapy (0.17 kg) resulted in negligible increase of body weight. Of note, teneligliptin added to metformin and canagliflozin resulted minimal reduction of body weight (− 0.40 and − 0.87 kg) [29, 32]. Cai et al. performed a meta-analysis on gliptins other than teneligliptin. They observed an increased body weight among the Asians and Caucasians (WMD 0.37 and 0.45 kg, respectively) [37].
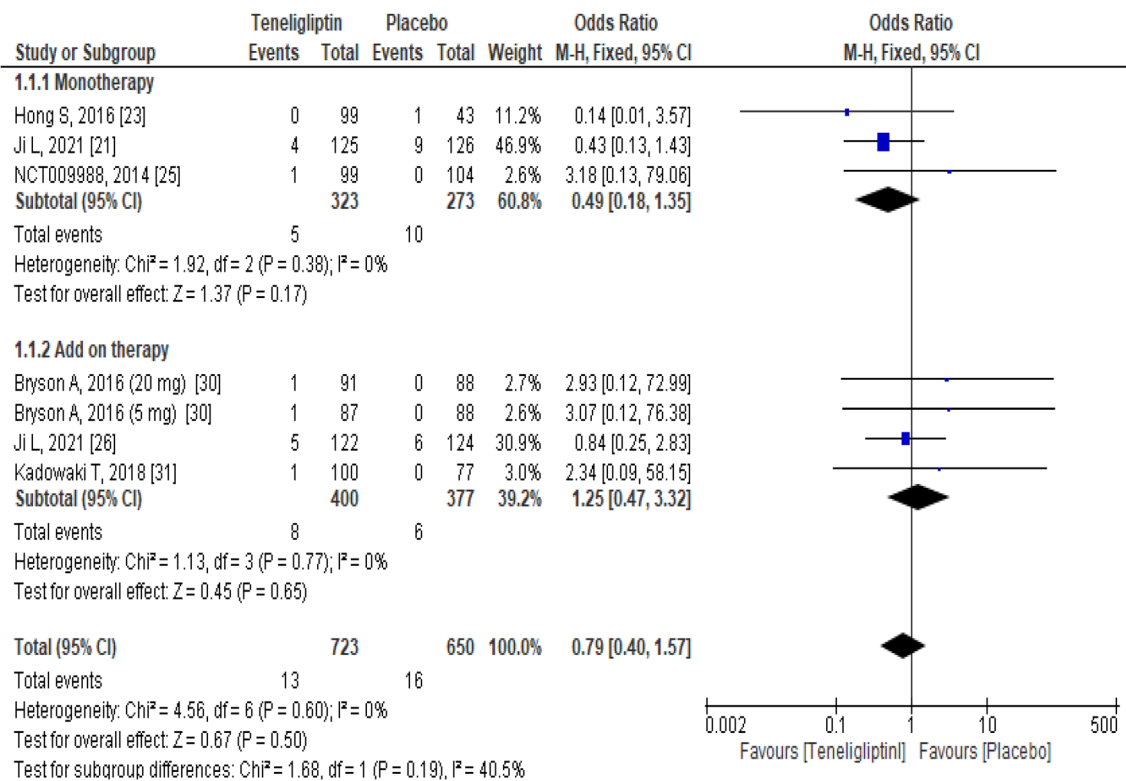
Fig. 4 Odds ratio for incidence of cardiovascular events: results are from Mantel–Haenszel fixed effects meta-analysis with a treatment arm continuity correction

Treatment with gemigliptin did not have a significantly different change in body weight after 12–24 weeks of therapy when compared to the placebo (WMD 0.84 kg) [38]. Teneligliptin resulted in less weight gain compared to gemigliptin. The high dose of semaglutide 2.4 mg, one of the approved [39] glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs), had resulted in significant weight loss [40], and GLP-1 RA are fair enough in reducing body weight compared to DPP-4Is [41]. In general, gliptins are associated with change of body weight, DPP-4Is are regarded as weight neutral with respect to change of body weight [42]. Weight gain can still occur when gliptins are given in combination with sulfonylureas [44, 45].

Patients treated with teneligliptin resulted in significant decrease in FPG levels, compared to placebo. The effect was superior in add-on therapy and the difference in groups was also significant ($P = 0.03$). The reduction of FPG levels was significant in both < 16 weeks and > 16 weeks of treatment with teneligliptin in sub-group analysis ($P < 0.00001$). The differences were also significant ($P = 0.05$) with high $I^2 = 75.1\%$. These findings are similar in previous meta-analysis ($P = 0.06$) [36]. In our review, glucose lowering capacity was higher in add-on therapy (WMD − 16.42 mg/dl) compared to monotherapy (WMD − 13.27 mg/dl). Cai and colleagues investigated the effect of DPP-4Is other
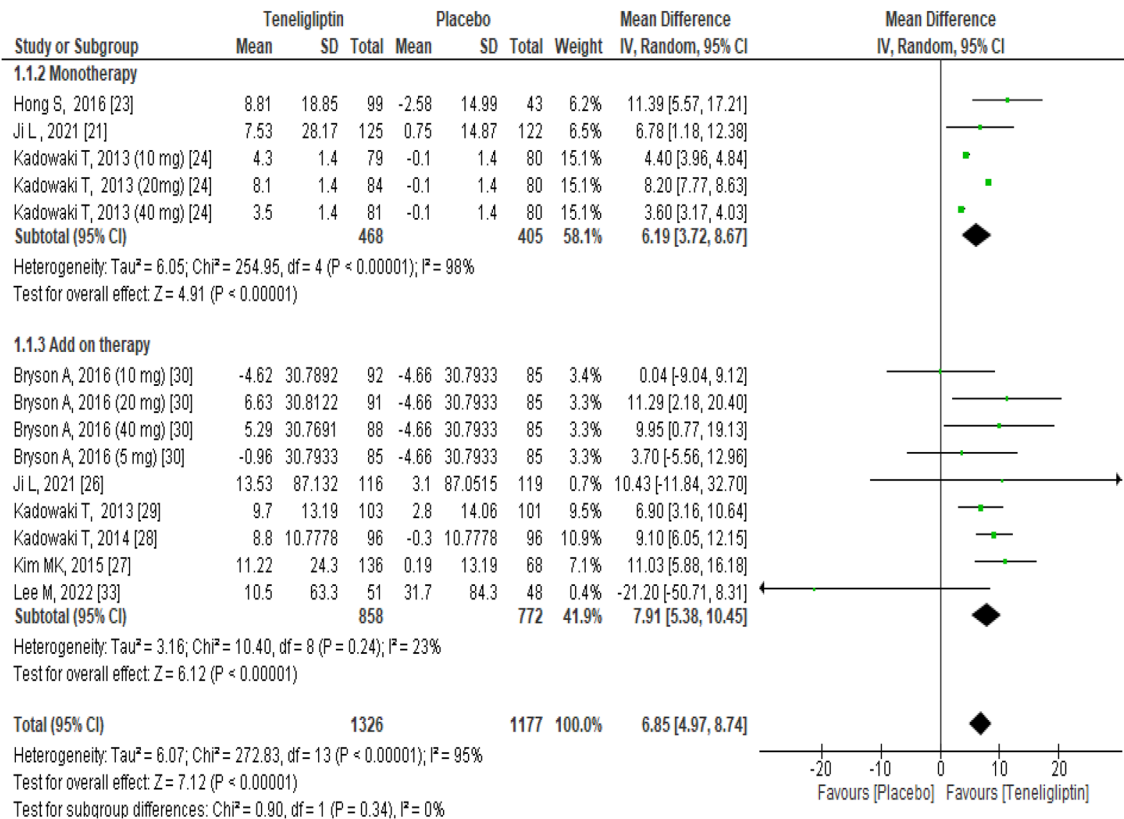
than teneligliptin on FPG levels. They noticed the WMD − 8.43 mg/dl; 95% CI − 20.14 to 3.27, ($P = 0.16$) among Asians and Caucasians. Our study reveals that teneligliptin effectively reduces the FPG levels compared to other gliptins [37]. Similarly, our results are also in concordance with gemigliptin meta-analysis conducted by Dutta et al. which stated that the treatment with gemigliptin showed significant reduction in FPG (WMD − 16.82 mg/dl) [38]. These findings were also quite similar with pioglitazone and add-on therapy with DPP-4Is (Sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin) WMD − 0.94 mmol/l (i.e., 16.93 mg/dl) [46]. Their results were similar with teneligliptin with pioglitazone (WMD − 16.50 mg/dl) [29]. Substantial reduction was noticed with teneligliptin added to glimepiride (WMD − 27.10 mg/dl) compared to other studies included in our review [28] which was certainly a greatest reduction compared to other anti-diabetic agents indicating that, sulfonyl urea antidiabetic agents are superior to thiazolidinediones. This could be due to difference in pharmacodynamics and duration of the study. In general, insulin secretagogues/sulfonylureas have a significant impact on FPG levels.

In view of improvement of β cells function, DPP-4Is have been linked to improved HOMA-β cells, making them a viable treatment option in early disease when patients still have adequate levels of β-cell function. The pathophysiology

of T2DM relies profoundly on β-cell destruction, and preserving β-cells slows disease progression [23]. In our study, treatment with teneligliptin as mono [21, 23, 24] and add-on therapy [26–30, 33] showed significant improvement of β cells function (WMD 6.19% and 7.91%); however, the difference between the groups was not significant (*P* = 0.34) (Fig. 5), the results were also similar in sub-group analysis between < 16 weeks and > 16 weeks of teneligliptin treatment (Supplementary Material Fig. D). Our findings are comparable to previous study conducted by Li and colleagues. In their review, teneligliptin increased the β-cells function by 9.31 (WMD 9.31, 95% CI 7.78–10.85; *P* < 0.00001), and results are represented in inverse variance Fixed-effects meta-analysis [36]. Similarly, DPP-4Is other than teneligliptin showed improved β-cell function in (WMD, 7.90) [37]. Takahashi et al. worked on DPP-4Is (except teneligliptin) and other oral hypoglycemic agents (OHAs) and observed that, gliptins are superior to alpha glucosidase inhibitors (α-GIs) but inferior to GLP-1 analogues in preservation of beta-cell function [47]. The varying of improvement of HOMA-β % was noticed with sitagliptin. The improvement was similar in sitagliptin 100 mg as mono and other active comparators (WMD 9.15% and 9.04%) [48], while in other review, sitagliptin 50 mg plus sulfonyl urea was superior (WMD 20.90; 95% CI − 10.02, 65.82) in improving HOMA-β% compared to sitagliptin 100 mg (WMD 5.40; 95% CI − 1.62; 12.42) [49]. Previous finding was also similar with sitagliptin 100 mg in mixed diabetic population of India, Chania, and Korea (WMD 5.4; 95% CI − 1.3 to 12.1, *P* > 0.05) [50]. DPP-4Is has significant impact on HOMA-β% among Asian and Caucasian diabetic patients and, Caucasians are well responders to DPP-4Is [51]. In our review teneligliptin plus metformin had highest improvement of HOMA-β% [23, 26, 27, 30]. However, there was no difference with 20 mg or 40 mg of teneligliptin alone or adding to other glycemic agents [24, 30]. In general, gliptins have insulin secretary function from pancreatic beta cells (incretin effect). gliptins could improve beta cell function directly or indirectly, but they are inferior to GLP-1 analogues in terms of preserving β-cell function [36].

HOMA model is employed in evaluation of pathophysiology of diabetes, which measures the β-cell function and insulin resistance (IR). In contrast to reduction of HOMA-IR, we examined nine studies, including three monotherapy [21, 23, 24] and six add-on therapy [26–30, 33] (Fig. 6). Patients treated with teneligliptin had significantly reduced IR in both groups compared to placebo, respectively. Mono therapy was inferior (WMD, − 0.17%) to add-on therapy (WMD

| Study or Subgroup | Teneligliptin | | | Placebo | | | Weight | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	IV, Random, 95% CI
1.1.2 Monotherapy									
Hong S, 2016 [23]	8.81	18.85	99	-2.58	14.99	43	6.2%	11.39 [5.57, 17.21]	
Ji L , 2021 [21]	7.53	28.17	125	0.75	14.87	122	6.5%	6.78 [1.18, 12.38]	
Kadowaki T, 2013 (10 mg) [24]	4.3	1.4	79	-0.1	1.4	80	15.1%	4.40 [3.96, 4.84]	
Kadowaki T, 2013 (20mg) [24]	8.1	1.4	84	-0.1	1.4	80	15.1%	8.20 [7.77, 8.63]	
Kadowaki T, 2013 (40 mg) [24]	3.5	1.4	81	-0.1	1.4	80	15.1%	3.60 [3.17, 4.03]	
Subtotal (95% CI)			468			405	58.1%	6.19 [3.72, 8.67]	
Heterogeneity: Tau² = 6.05; Chi² = 254.95, df = 4 (P < 0.00001); I² = 98%									
Test for overall effect: Z = 4.91 (P < 0.00001)									
1.1.3 Add on therapy									
Bryson A, 2016 (10 mg) [30]	-4.62	30.7892	92	-4.66	30.7933	85	3.4%	0.04 [-9.04, 9.12]	
Bryson A, 2016 (20 mg) [30]	6.63	30.8122	91	-4.66	30.7933	85	3.3%	11.29 [2.18, 20.40]	
Bryson A, 2016 (40 mg) [30]	5.29	30.7691	88	-4.66	30.7933	85	3.3%	9.95 [0.77, 19.13]	
Bryson A, 2016 (5 mg) [30]	-0.96	30.7933	85	-4.66	30.7933	85	3.3%	3.70 [-5.56, 12.96]	
Ji L, 2021 [26]	13.53	87.132	116	3.1	87.0515	119	0.7%	10.43 [-11.84, 32.70]	
Kadowaki T, 2013 [29]	9.7	13.19	103	2.8	14.06	101	9.5%	6.90 [3.16, 10.64]	
Kadowaki T, 2014 [28]	8.8	10.7778	96	-0.3	10.7778	96	10.9%	9.10 [6.05, 12.15]	
Kim MK, 2015 [27]	11.22	24.3	136	0.19	13.19	68	7.1%	11.03 [5.88, 16.18]	
Lee M, 2022 [33]	10.5	63.3	51	31.7	84.3	48	0.4%	-21.20 [-50.71, 8.31]	
Subtotal (95% CI)			858			772	41.9%	7.91 [5.38, 10.45]	
Heterogeneity: Tau² = 3.16; Chi² = 10.40, df = 8 (P = 0.24); I² = 23%									
Test for overall effect: Z = 6.12 (P < 0.00001)									
Total (95% CI)			1326			1177	100.0%	6.85 [4.97, 8.74]	
Heterogeneity: Tau² = 6.07; Chi² = 272.83, df = 13 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 7.12 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%									

-20 -10 0 10 20
Favours [Placebo] Favours [Teneligliptin]

Fig. 5 Weighted mean difference in change from baseline in HOMA-β (%): teneligliptin versus placebo or active comparators. Results are from inverse variance random-effects meta-analysis

− 0.27%) in reversal of IR. While, but the sub-group difference was not significant (P = 0.46). These findings were also similar in sub-groups between < 16 weeks and > 16 weeks of treatment with teneligliptin (P = 0.36, $I^2 = 0\%$) (Supplementary Material Fig. E). Teneligliptin 40 mg plus metformin had superior efficacy (WMD − 1.04%) [30] than teneligliptin 40 mg alone (WMD − 0.30%) [24] in reduction of IR, respectively. Our findings are comparable to those of Li et al. They revealed that teneligliptin add-on therapy (WMD − 0.06%) outperformed monotherapy (WMD − 0.25%). In monotherapy, WMD was − 0.12% compared to placebo [36]. Similarly, Lyu et al. mentioned that DPP-4 inhibitors (other than teneligliptin) as monotherapy or as add-on therapy significantly improved β-cell function but had no significant effect on insulin resistance in T2DM [52]. Add on therapy with sitagliptin 100 mg showed insignificant reduction of IR and significant decrease in glycemic parameters [48], whereas our findings are significant in both groups. The differences in outcomes may be attributable to ethnic differences and dietary factors and meal standardisation. However, interpretation of these HOMA indices needs caution. The included studies in the current review do not state whether the subjects had dyslipidaemia, hypertension, or hyperuricemia along with type 2 diabetics. As a result, the reliability and interpretation of HOMA indices are uncertain [53]. Yet, HOMA-IR is an independent predictor of CVD in type 2 diabetes. The improvement of insulin resistance might have beneficial effects not only on glucose control but also on CVD in patients with type 2 diabetes [54].

The overall effect of teneligliptin treatment had significant decrease in HbA_{1c} levels (WMD − 0.68%). Compared to monotherapy (WMD − 0.88%) add-on therapy showed less reduction (WMD − 0.62%) of HbA_{1c} levels. The change of HbA_{1c} levels was also similar in sub-group analysis, and these results are supported by the previous studies. Gliptins as monotherapy reduced HbA_{1c} levels better than combination with other anti-diabetic agents [55–57]. The present results were also comparable to those of gemigliptin. According to the review, gemigliptin treatment resulted in a significantly greater reduction in HbA1c (WMD − 0.91%) [38]. Similarly, Dutta et al. evaluated the effect of evogliptin in patients with T2DM. Evogliptin was not inferior to sitagliptin or linagliptin in terms of HbA1c reduction (WMD, 0.06%) at 12 and 24 weeks (WMD 0.57%) at follow-up. However, it was superior to placebo at 12 and 24 weeks (WMD 0.57% and 0.22%), respectively [43]. Wang et al.
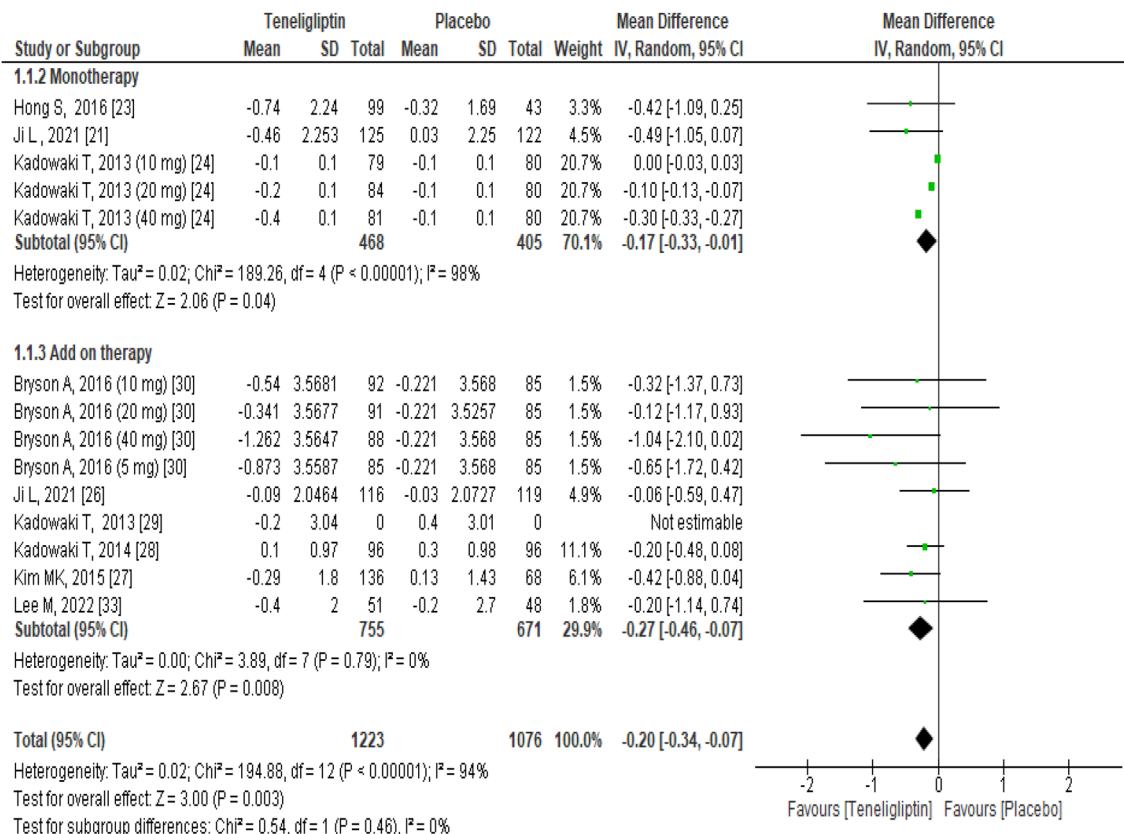
Fig. 6 Weighted mean difference in change from baseline in HOMA-IR: teneligliptin versus active comparators. Results are from inverse variance random-effects meta-analysis

investigated on pioglitazone as mono-therapy and add-on therapy with DPP-4Is other than teneligliptin. When compared to pioglitazone alone, DPP-4Isand pioglitazone combination therapy was associated with a greater reduction in HbA_{1c} (WMD − 0.64%) [46]. He et al. also worked on DPP-4Is (other than teneligliptin) add-on to active comparators and found minimal WMD, 0.26% with DPP-4Is [58]. Similarly, Wang et al. conducted a review on omarigliptin and reported that omarigliptin significantly reduced HbA_{1c} levels when compared to other OHAs (WMD 0.38%) [59]. In contrast to our findings, teneligliptin as monotherapy had a better reduction of HbA1c levels, i.e., WMD, − 0.88%, than add-on therapy. This variation could be due to a difference in duration of diabetes. The current study included add-on therapy studies that lasted more than 6 years. HbA1c reduction is unlikely to be greater than 1.5% during the first 6 months of treatment. Pre-treated HbA1c levels have modest effect on reduction of HbA1c in response to therapy, while teneligliptin 40 mg as mono or add on therapy had no differences [24, 29, 30].

The reason, while treating patients with diabetes, it is difficult to achieve and maintain recommended glycemic targets without causing adverse cardiovascular (CV) and hypoglycemic effects. Probably, DPP-4Is are safer and are associated with a low risk of hypoglycaemic episodes and weight gain when compared to other antidiabetic agents. Hence, these are advocated for hyperglycaemic individuals with high risk of hypoglycemia [60]. In the present study, the difference in hypoglycemic incidence between teneligliptin and placebo was not significant ($P > 0.05$), regardless of duration of therapy. Our findings are similar, in contrast to hypoglycemic episodes with DPP-4Is. In a Swedish study, patients taking both metformin and sulphonyl ureas (SU) have higher risk of severe hypoglycemia, compared to those taking DPP-4Is [61]. Hypoglycemia is still possible when gliptin is combined with SU [44, 45]. The risk was also high in linagliptin and sitagliptin when combined with insulin or insulin secretagogues compared to placebo [62].

In our review, there is no significant CV risk difference among the teneligliptin treated groups compared to placebo, despite of treatment duration. Our findings are supported by other studies. Several cardio vascular outcome trials (COVT) have been studied with DPP-4 Is. Sinha et al. were reviewed five available COVT with DPP-4i; SGLT2-i and GLP1-RA. DPP-4Is and reported that SGLT2-i were associated with neutral effect on myocardial infraction (MI), stroke, hospitalization due to heart failure (hHF) and CV death compared to placebo ($P > 0.05$). The class of GLP1-RA had significantly reduced the risk of atherosclerotic cardio vascular disease (ASCVD), such as MI and stroke [63], whereas DPP-4Is were not associated with hHF [64]. However, while sitagliptin was associated with a neutral CV risk in a pooled analysis, SUs was associated with a higher rate of CV-related events

in a sub-group analysis [65]. Besides this, in both RCTs and cohort studies, the CV safety of SU appears to be lower than that of DPP-4Is [66]. While, in our review, CV events are not observed in patients treated with SU plus teneligliptin [28, 33]. The CV safety was also assessed in Swedish diabetics, and a higher risk of CV complications and all-cause mortality was observed in those who had taken both biguanides and SU compared to those who took biguanides and DPP-4Is. However, teneligliptin was not included in their study [61]. The long-term effects of DDP-4Is were associated with low risk of MI than SU and this outcome was similar with GLP-1RAs [67]. During 641 days of follow-up, teneligliptin therapy was not associated with an increased risk of CV events including hHF and lower risk of hypoglycemia compared to SU therapy [68], similarly DPP-4Is (not included teneligliptin) showed no significant effects on CV mortality [64, 69]. However, compared to DPP-4i treatment, insulin initiation was associated with an increased risk of all-cause mortality, fatal and nonfatal CVD, and severe hypoglycemia [70]. Which indicated that the DPP-4Is are safer in patients of T2DM with CV disorders. To strengthen and update the existing evidence on teneligliptin, extensive RCTs with longer durations on diverse T2DM populations are required.

On detailed analysis, the strengths of this meta-analysis include the incorporation of direct evidence from recently published high-quality RCTs which are assessed for the efficacy and safety of teneligliptin. Considering, treatment duration and other factors may affect the outcomes of the study, hence subgroup meta-analysis was conducted. Nevertheless, it is also necessary to acknowledge certain limitations. First, it was difficult to avoid certain heterogeneity, irrespective of performing sub-group analysis. Second, teneligliptin monotherapy clinical trials are shorter (< 24 weeks) hence, long term studies are required to assess the long-term benefits and risks of teneligliptin alone and in combination with other hypoglycemic drugs. Third, the included studies did not provide sufficient data for meta-analysis. In addition, teneligliptin is well-tolerated. However, our study evaluated only the risk of hypoglycemia and cardiovascular safety among the included studies, as this is the outcome in which we were interested. Based on currently available data from a limited number of RCTs, combination therapy effective in the improvement of beta cell function and reduction of glucose levels, thus offering a valuable option for T2DM patients with inadequate glycemic control on monotherapy. Of note, our inferences are based on data from RCTs that were not designed to assess these outcomes.

Conclusions

In conclusion, our study has demonstrated efficacy and safety profile of teneligliptin as mono or add-on therapy with other glycemic agents which have good response in

type 2 diabetes patients. Teneligliptin showed statistically significant improvement in FPG levels, β cell functioning, IR, and HbA$_{1c}$ % compared to placebo. Teneligliptin had no impact on reduction of body weight. Furthermore, the adverse outcomes are not significant in patients treated with teneligliptin alone or combination with other agents compared to placebo. However, additional large-scale, high-quality, long-term follow-up clinical trials are needed to confirm the long-term effectiveness and safety with teneligliptin.

Declarations

Conflict of interest The authors declare no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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