

Is tirzepatide 15 mg the preferred treatment strategy for type 2 diabetes? A meta-analysis and trial-sequence-analysis

X.-Y. YANG¹, S. YIN¹, Y.-F. YU^{1,2}, G. HU², F.-Z. HANG¹, M.-L. ZHOU¹, P. LIU¹, W.-X. JIAN¹

¹College of Chinese Medicine, Hunan University of Chinese Medicine, Changsha, Hunan, China

²The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, China

Xinyu Yang, Shuang Yin, and Yunfeng Yu contributed equally to this work

Abstract. – OBJECTIVE: The study aims to evaluate tirzepatide's efficacy and safety in treating type 2 diabetes by meta-analysis and trial-sequential-analysis (TSA).

MATERIALS AND METHODS: Eight databases were searched for clinical trials on tirzepatide for type 2 diabetes with a time limit of November 2022. Revman5.3 and TSA 0.9.5.10 Beta were selected for meta-analysis and TSA.

RESULTS: Compared with placebo, the meta-analysis demonstrated that tirzepatide 15 mg reduced hemoglobin-type-A1C (HbA1c) ($p<0.00001$), fasting-serum-glucose (FSG) ($p<0.00001$), and weight ($p<0.00001$). Compared with insulin, tirzepatide 15 mg reduced HbA1c ($p<0.00001$), FSG ($p<0.00007$), and weight ($p<0.00001$). Compared with glucagon-like-peptide-1 receptor-agonist (GLP-1 RA), tirzepatide 15 mg reduced HbA1c ($p=0.00004$), FSG ($p=0.001$), and weight ($p<0.00001$). In safety endpoints, the meta-analysis revealed that adverse events (AEs) of placebo, insulin and GLP-1 RA were comparable to tirzepatide 15 mg. The total AEs ($p=0.02$) and gastrointestinal (GI) AEs ($p=0.03$) were higher in tirzepatide 15 mg than in the placebo, while hypoglycemia (<54 mg/dl) was comparable. The major adverse cardiovascular events-4 (MACE-4) ($p=0.03$) and hypoglycemia (<54 mg/dl) ($p<0.00001$) of tirzepatide 15 mg were lower when compared to insulin, while total AEs ($p=0.03$) were increased. Compared with GLP-1 RA, tirzepatide 15 mg was comparable in safety endpoints in total AEs and GI AEs, while hypoglycemia (<54 mg/dl) ($p=0.04$) was higher. TSA indicated that HgA1c, FSG, and weight benefits were conclusive. In safety endpoints, only MACE-4 and hypoglycemia (<54 mg/dl) of Tirzepatide 15 mg vs. Insulin were conclusive. Harbord regression of AEs suggested no evident publication bias ($p=0.618$).

CONCLUSIONS: Tirzepatide 15 mg reduced HbA1c and weight more effectively than placebo,

insulin, and GLP-1 RA. Total AEs were higher than placebo and insulin but comparable to GLP-1 RA. Tirzepatide 15 mg is a kind of optimal strategy to treat type 2 diabetes. However, there is a need to focus on GI AEs.

Key Words:

Tirzepatide, Type-2-diabetes, Meta-analysis, Trial-sequential-analysis, Insulin, Glucagon-like-peptide-1 receptor-agonist.

Introduction

Type 2 diabetes is a chronic progressive disease characterized by hyperglycemia, insulin resistance (IR), and impaired islet cell function, strongly associated with microvascular and macrovascular complications and increased cardiovascular mortality¹. According to epidemiology, the global prevalence of diabetes in 2019 was estimated to be 9.3% (463 million people), and 50.1% of people with diabetes were unaware of their diabetes². Type 2 diabetes is the leading cause of cardiovascular disease, kidney disease, blindness in adults, and lower limb amputation³, which seriously affects the physical and mental health of diabetic patients. As a result, this disease has become a significant public health burden worldwide⁴. Being overweight or obese is one of the major modifiable risk factors for type 2 diabetes³, and numerous studies^{3,5,6} have shown a positive association between body mass index (BMI) and the risk of type 2 diabetes. Most cells in obese patients, especially adipocytes, are insensitive to insulin, thus leading to insulin resistance to some extent⁶. IR, in turn, is a critical factor in the development

and progression of type 2 diabetes and a cause of poor glycemic control in type 2 diabetes patients⁷.

Patients with type 2 diabetes mainly aim to lower glycemic and weight by interfering with diet, changing living habits, or using drugs such as insulin, glucagon-like-peptide-1 receptor-agonist (GLP-1 RA), and even choosing metabolic surgery when necessary⁷. As type 2 diabetes advances, some patients may require insulin treatment as other medications may no longer be sufficient. At this stage, the use of insulin to control glycemic in patients is of vital importance⁸. Nevertheless, insulin can increase the risk of hypoglycemic episodes, and hypoglycemia is the main obstacle to restoring normoglycemia in patients with type 2 diabetes. Therefore, a balance between good glycemic control and the risk of hypoglycemia must be managed in treating type 2 diabetes⁹. GLP-1 RA can exert glycemic control, reduce weight, and improve cardiovascular risk factors, and it is now a widely recommended hypoglycemic medicine^{10,11}. However, many patients with type 2 diabetes still fail to achieve optimal levels of glycemic control⁷. Moreover, the weight loss achieved with these drugs is insignificant and distinctly lower than what can be accomplished with bariatric surgery¹². Treating type 2 diabetes necessitates the development of a new hypoglycemic medication that can decrease both hemoglobin-type-A1C (HbA1c) levels and weight.

Tirzepatide is a dual gastric inhibitory polypeptide (GIP) and GLP-1 RA composed of 39 amino acid synthetic peptides and has a good hypoglycemic effect¹³. Previous studies^{13,14} have shown that tirzepatide can effectively reduce HbA1c, and its hypoglycemic effect is increased in a dose-dependent manner. In the latest phase 3 clinical trial¹⁵ in patients with type 2 diabetes, tirzepatide reduced HbA1c by 26.0 mmol/mol to 30.8 mmol/mol. Furthermore, in patients treated with tirzepatide 15mg, 79% of patients' HbA1c fell below 39.0 mmol/mol (5.7%), the American Diabetes Association's normoglycemic threshold¹⁵. The results demonstrated the excellent glucose-lowering effect of tirzepatide 15 mg. In comparison, only 51% and 58% of participants were treated with tirzepatide 5 mg, and tirzepatide 10 mg returned to normoglycemia. Recent studies^{13,15,16} also showed that tirzepatide 15 mg is the best intervention for weight control, which seems to mean that tirzepatide 15 mg is the best strategy for treating diabetes. In order to clarify whether the specific benefits of tirzepatide 15 mg

for patients with type 2 diabetes are consistent with previous research results¹³⁻¹⁵, we conducted search screening and meta-analysis on published randomized controlled trials of tirzepatide 15 mg in the treatment of type 2 diabetes. Compared with previous studies^{14,16}, the number of included studies in this meta-analysis has increased, with the largest sample size of a single-dose study of tirzepatide 15 mg. In addition, trial-sequential-analysis (TSA) has been adopted to correct the meta-analysis results further, making the research results more scientific and reliable.

Materials and Methods

This study has been registered in PROSPERO (Registration Number: CRD42023398927; <https://www.crd.york.ac.uk/prospero/#recordDetails>). It strictly followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) for systematic reviews and meta-analyses¹⁷.

Literature Search

The databases of the China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), VIP, Wanfang, Embase, PubMed, the Cochrane Library, and Web of Science were retrieved for clinical trials on tirzepatide for type 2 diabetes with a time limit to November 2022. The English subject headings covered tirzepatide and type-2-diabetes, and the Chinese subject headings covered tirzepatide and *erxingtangniaobing* (the Chinese name of type-2-diabetes). Based on the subject terms, the Chinese free terms were expanded by CNKI and CBM databases. The Medical Subject Headings (MeSH) database expanded the English free terms, and then the subject terms and free terms were combined for searching.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows. 1) Type of studies: only randomized controlled trials. 2) Participants: in line with the basic diagnosis of type 2 diabetes¹⁸. 3) Interventions: patients in the experimental group took tirzepatide, while those in the control group took a placebo or other hypoglycemic agents. 4) Outcomes: hemoglobin-type-A1C (HbA1c), fasting-serum-glucose (FSG), and weight were treated as efficacy endpoints. Total adverse events (AEs), serious AEs, gastrointestinal (GI) AEs, major adverse cardio-

vascular events-4 (MACE-4), and hypoglycemia (<54 mg/dl) were used as safety endpoints.

The exclusion criteria were as follows. 1) Studies such as reviews, animal experiments, and case reports. 2) Studies published repeatedly. 3) Studies published in abstract form. 4) Studies with incomplete or unclear data.

Literature Screening, Data statistics, and Risk of Bias

In the first step, the base literature retrieved from each database was imported into Endnote X9 software (The Thomson Scientific, Downtown Stamford, CT, USA), and duplicates were excluded. Then, after reading the titles and abstracts and reviewing the complete text, the included literature was finalized by eliminating irrelevant literature based on the inclusion criteria. Next, the included literature was categorized, and basic characteristics such as author, year, sample size, mean age, sex ratio, intervention, and duration of treatment were extracted and recorded in the statistical data table. Finally, the risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool (The Copenhagen Trial Unit, Copenhagen, Denmark) based on the requested entries. All work was independently conducted by two investigators, and any disagreements were resolved by a third investigator.

Statistical Analysis

Meta-analysis was conducted using RevMan5.3 software (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark). Risk ratio (RR) and 95% confidence interval (95% CI) were used as effect sizes for dichotomous variables. Continuous variables used mean difference (MD) and 95% CI as effect sizes. Heterogeneity was analyzed using the I^2 test and Q test. If $I^2 < 50\%$ and $p > 0.1$, the heterogeneity was small and fixed-effect model (FEM) analysis was implemented. Otherwise, random effects model (REM) analysis was employed. For indicators with significant heterogeneity, sensitivity analysis was used, in which the remaining studies were combined for analysis after excluding one study at a time. If there was no noticeable change in the continuous variables obtained from each combined analysis, the results were suggested to be robust. TSA0.9.5.10 Beta software (The Copenhagen Trial Unit, Copenhagen, Denmark) performed the TSA. The original results were conclusive if the cumulative Z value crossed the required information size (RIS) or TSA bound. Publication bias was assessed using Stata15.0

software (Stata Corp LLC, College Station, TX, USA). If Harbord regression demonstrated $p > 0.1$, there was no publication bias.

Results

Literature Search Results

A total of 376 articles were retrieved. Then, 188 duplicates were removed, and 179 were excluded after reading the title, abstract, and full text. Finally, 9 articles^{15,19-26} were included (Figure 1).

Basic Materials

Finally, 9 clinical studies were included, with a total sample size of 4,148 cases, 1,722 cases in the experimental group, and 2,426 cases in the control group. The study centers were located on 5 continents, including North America, South America, Europe, Asia, and Oceania. 5 studies¹⁹⁻²³ reported “tirzepatide vs. placebo” in 735 cases. 2 studies^{24,25} reviewed “tirzepatide vs. insulin” in 2057 cases. 4 studies^{15,19,25,26}, totaling 1454 cases, investigated “tirzepatide vs. GLP-1 RA”. The basic characteristics of the included studies are shown in Table I.

Risk of Bias Assessment

Of the 9 included studies, all areas were at low risk of bias except for Del et al²⁴, Ludvik et al²⁵, and Frias et al²⁶, which were at high risk of blinding participants and personnel. The risk of bias for the included studies is shown in Figure 2.

Efficacy Endpoints

Tirzepatide 15 mg vs. placebo

Five studies¹⁹⁻²³ were included to compare the efficacy endpoint of “tirzepatide 15mg vs. placebo”. Meta-analysis demonstrated that HbA1c (MD -1.88, 95% CI -2.04 – -1.72, $p < 0.00001$), FSG (MD -51.46, 95% CI -68.76 – -34.15, $p < 0.00001$) and weight (MD -9.73, 95% CI -12.25 – -7.21, $p < 0.00001$) were significantly lower in tirzepatide 15 mg than the placebo. TSA indicated that these benefits observed in the current information set were conclusive. In addition, sensitivity analysis showed that the combined sensitivity of FSG and weight were low, and the results were robust (Figure 3).

Tirzepatide 15 mg vs. insulin

Two studies^{24,25} were included to evaluate the efficacy endpoint of “tirzepatide 15 mg vs. insulin”.

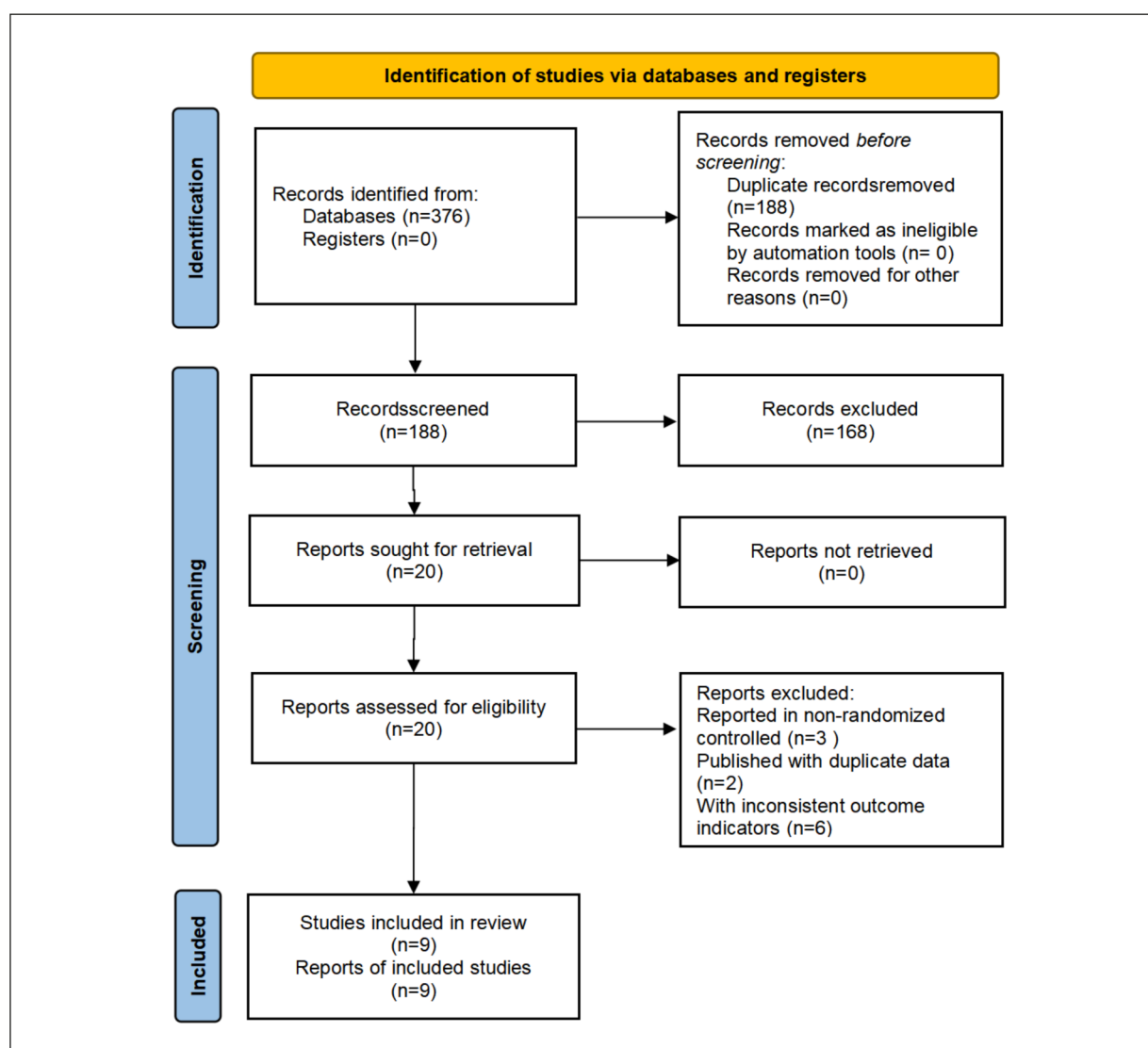


Figure 1. Study flow diagram.

Meta-analysis revealed that HbA1c (MD -1.09, 95% CI -1.18 – -1.00, $p<0.00001$), FSG (MD -5.91, 95% CI -9.32 – -2.50, $p<0.00007$), and weight (MD -14.36, 95% CI -15.93 – -12.79, $p<0.00001$) were dramatically lower in tirzepatide 15 mg compared with the insulin. TSA displayed that the HbA1c, FSG, and weight observed in the current information set were conclusive (Figure 4).

Tirzepatide 15 mg vs. GLP-1 RA

Four studies^{15,19,22,26} were included to analyze “tirzepatide 15 mg vs. GLP-1 RA”. Meta-analysis suggested that HbA1c (MD -1.17, 95% CI -1.83 – -0.52, $p=0.00004$), FSG (MD -22.97, 95%CI -37.01 – -8.93, $p=0.001$), and weight (MD -7.41, 95% CI -10.01 - -4.80, $p<0.00001$) were significantly lower in tirzepatide 15 mg than GLP-1 RA.

TSA demonstrated that the HbA1c, FSG, and weight improvements observed in the current data set were conclusive for each group. Sensitivity analysis showed that the combined sensitivity of HbA1c, FSG, and weight was low, and the results were robust (Figure 5).

Safety Endpoints

Tirzepatide 15 mg vs. placebo

Five studies¹⁹⁻²³ were included to compare the safety endpoints of “tirzepatide 15 mg vs. placebo”. Meta-analysis indicated that total AEs (RR 1.22, 95% CI 1.04-1.44, $p=0.02$) and GI AEs (RR 3.59, 95% CI 1.16-11.17, $p=0.03$) were significantly higher in tirzepatide 15 mg compared to the

Table I. Table of basic characteristics of the included studies.

Author Name	Research Center	Patient Number	Treatment Duration (weeks)	Intervention	Number Randomized	Male N (%)	Age (Years)	Disease Duration (years)	HbA1c (%)	Body weight (kg)
Frias et al ¹⁹	Poland, Slovakia, Puerto Rico, USA	158	26	TZP 15 mg	53	22 (42%)	56.0	8.5	8.1	89.1
Frias et al ²⁰	USA	82	12	dulaglutide 1.5 mg	54	24 (44%)	58.7	9.3	8.1	89.8
				Placebo	51	29 (57%)	56.6	8.6	8.0	91.5
				TZP 15 mg-1	28	16 (57%)	55.5	8.2	8.5	88.7
				TZP 15 mg-2	28	23 (82%)	56.6	8.9	8.4	89.6
				Placebo	26	12 (46%)	56.0	8.8	8.2	89.6
Rosenstock et al ²¹	India, Japan, Mexico, USA	236	40	TZP 15 mg	121	63 (52%)	52.9	4.8	7.9	85.4
Heise et al ²²	Germany	117	28	Placebo	115	56 (49%)	53.6	4.5	8.1	84.8
				TZP 15 mg	45	31 (69%)	61.1	10.2	7.8	94.2
				Semaglutide 1 mg	44	34 (77%)	63.7	12.7	7.7	92.7
Dahl et al ²³	USA, Japan, Czech Republic, Germany, Poland, Slovakia, Puerto Rico, Spain	240	40	Placebo	28	21 (75%)	60.4	11.0	7.9	98.7
				TZP 15 mg	120	65 (54%)	61.0	13.7	8.2	96.2
				Placebo	120	66 (55%)	60.0	12.9	8.4	94.1
Del et al ²⁴	Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russia, Slovakia, Spain, Taiwan, USA	1338	52	TZP 15 mg	338	203 (60%)	63.7	10.4	8.5	90.0
				Insulin glargine	1,000	636 (64%)	63.8	10.7	8.5	90.2
Ludvik et al ²⁵	Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea, Spain, Taiwan, Ukraine, USA	719	52	TZP 15 mg	359	194 (54%)	57.5	8.5	8.2	94.9
				Insulin degludec	360	213 (59%)	57.5	8.1	8.1	94.0
Frias et al ²⁶	USA, UK, Argentina, Australia, Brazil, Canada, Israel, Mexico	939	40	TZP 15 mg	470	214 (45%)	55.9	8.7	8.3	93.8
Inagaki et al ¹⁵	Japan	319	52	Semaglutide 1 mg	469	225 (48%)	56.9	8.3	8.3	93.7
				TZP 15 mg	160	132 (83%)	56.0	5.1	8.2	78.9
				dulaglutide 0.75 mg	159	117 (74%)	57.5	5.0	8.2	76.5

*N: number; HbA1c: hemoglobin-type-A1C; TZP: tirzepatide.

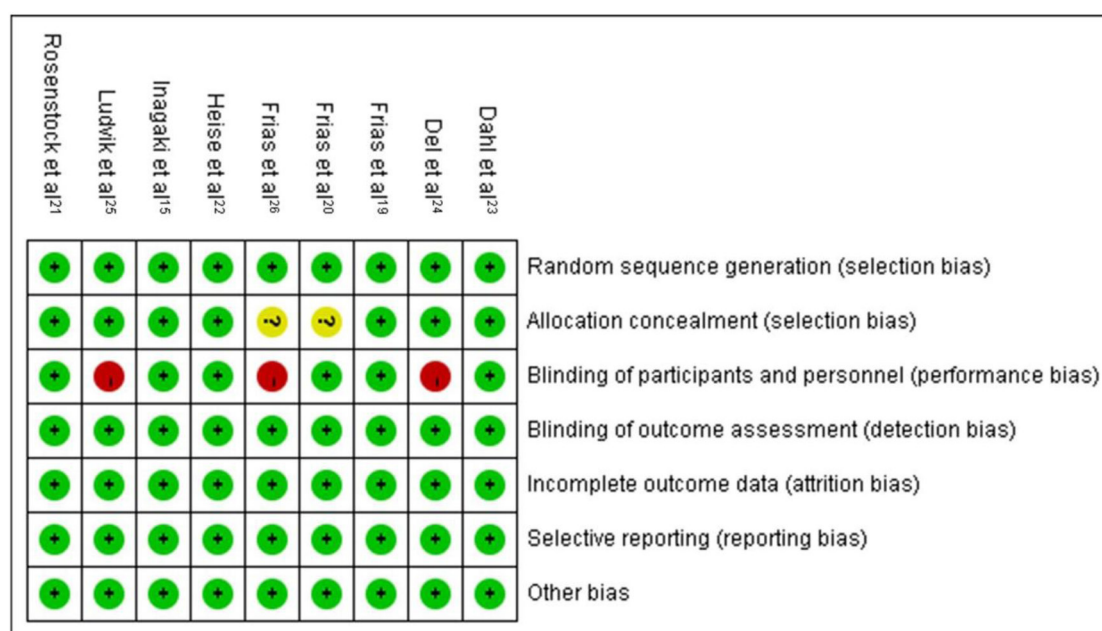


Figure 2. Risk of bias graph.

placebo, while serious AEs (RR 0.72, 95% CI 0.36-1.45, $p=0.36$) and hypoglycemia (<54 mg/dl) (RR 1.06, 95% CI 0.56-1.98, $p=0.86$) were comparable. TSA showed that these results were inconclusive. Sensitivity analysis showed that the combined sensitivity of total AEs was low, and the results were robust (Table II).

Tirzepatide 15 mg vs. insulin

Two studies^{24,25} were included to compare the safety endpoints of “tirzepatide 15 mg vs. insu-

lin”. Meta-analysis indicated that the MACE-4 (RR 0.51, 95% CI 0.28-0.93, $p=0.03$) and hypoglycemia (<54 mg/dl) (RR 0.39, 95% CI 0.28-0.56, $p<0.00001$) were significantly lower in the tirzepatide 15 mg. The total AEs (RR 1.24, 95% CI 1.02-1.50, $p=0.03$) were significantly higher for tirzepatide 15 mg than insulin, while the serious AEs (RR 0.83, 95% CI 0.45-1.53, $p=0.55$) in tirzepatide 15 mg were comparable to insulin. TSA showed that the MACE-4 and hypoglycemia benefits of tirzepatide 15 mg we-

Table II. Meta-analysis and TSA results of tirzepatide 15mg vs. placebo, insulin, and GLP-1 RA for AEs.

Outcome	TZP arm	Control arm	P	RR (95% CI)	TSA
TZP 15 mg vs. Placebo					
Total AEs	302/395	219/340	63	1.22 (1.04, 1.44)	No
Serious AEs	13/395	17/340	0	0.72 (0.36, 1.45)	No
GI AEs	85/174	27/166	82	3.59 (1.16, 11.17)	No
Hypoglycemia (<54 mg/dl)	17/297	16/216	0	1.06 (0.56, 1.98)	No
TZP 15 mg vs. Insulin					
Total AEs	522/697	872/1360	87	1.24 (1.02, 1.50)	No
Serious AEs	67/697	215/1360	74	0.83 (0.45, 1.53)	No
MACE-4	12/697	65/1,360	0	0.51 (0.28, 0.93)	Yes
Hypoglycemia (<54 mg/dl)	35/697	217/1,360	0	0.39 (0.28, 0.56)	Yes
TZP 15 mg vs. GLP-1 RA					
Total AEs	546/728	507/726	50	1.05 (0.97, 1.13)	No
Serious AEs	37/728	30/726	59	1.06 (0.41, 2.76)	No
GI AEs	257/683	217/682	75	1.43 (0.87, 2.34)	No
Hypoglycemia (<54 mg/dl)	10/630	2/628	0	4.19 (1.06, 16.56)	No

*TZP: tirzepatide; RR: Risk ratio; TSA: Trial sequential analysis; AEs: adverse events; GI: gastrointestinal; MACE-4: major adverse cardiovascular events-4.

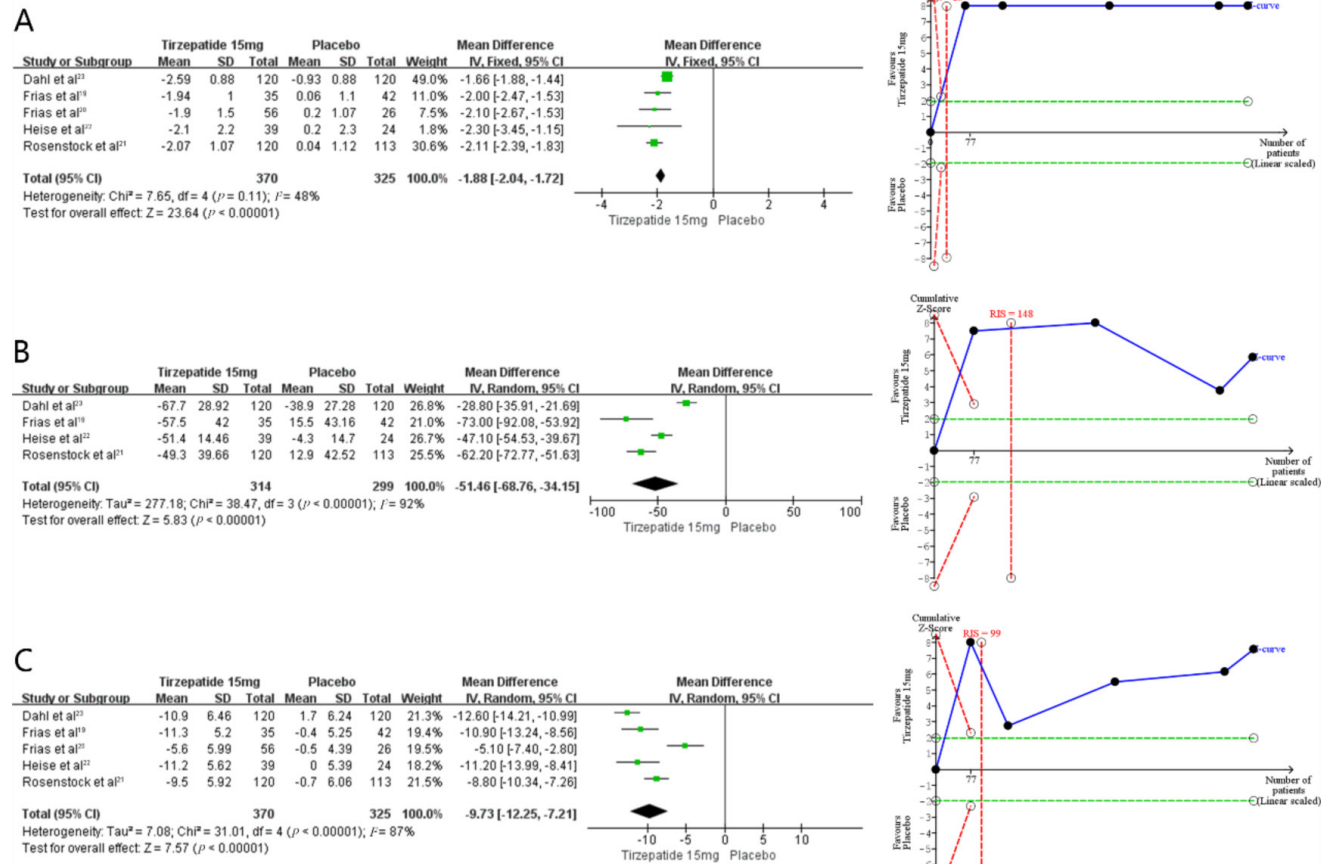


Figure 3. Meta-analysis and TSA results of efficacy endpoints in tirzepatide 15 mg vs. placebo in the treatment of type 2 diabetes. **A**, Meta-analysis and TSA results of HbA1c in tirzepatide 15 mg vs. placebo in the treatment of type 2 diabetes. **B**, Meta-analysis and TSA results of FSG in tirzepatide 15 mg vs. placebo in the treatment of type 2 diabetes. **C**, Meta-analysis and TSA results of weight in tirzepatide 15 mg vs. placebo in the treatment of type 2 diabetes.

Is tirzepatide 15 mg the preferred treatment strategy for type 2 diabetes?

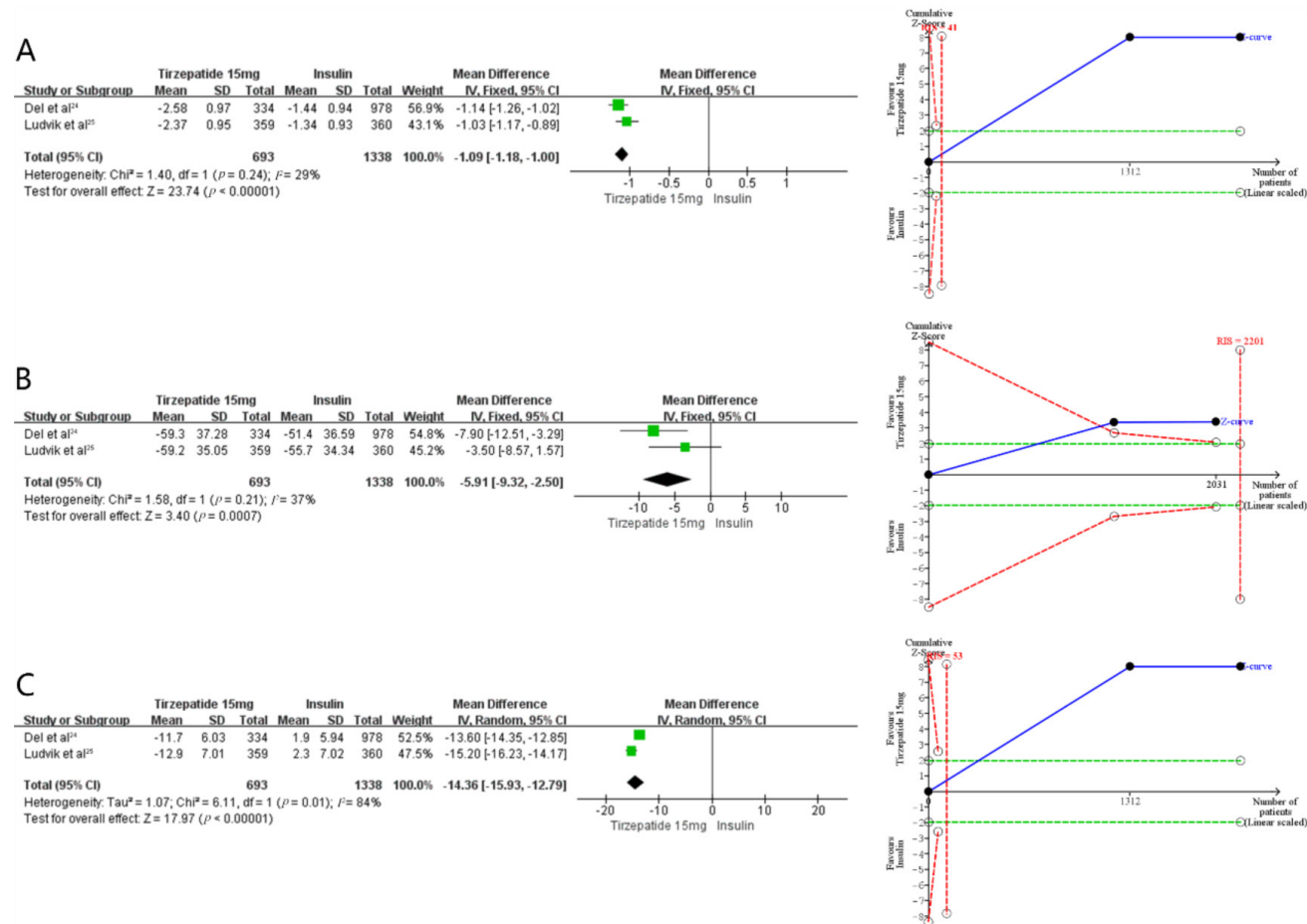


Figure 4. Meta-analysis and TSA results of efficacy endpoint in tirzepatide 15 mg vs. insulin in treating type 2 diabetes. **A**, Meta-analysis and TSA results of HbA1c in tirzepatide 15 mg vs. insulin in the treatment of type 2 diabetes. **B**, Meta-analysis and TSA results of FSG in tirzepatide 15 mg vs. insulin in the treatment of type 2 diabetes. **C**, Meta-analysis and TSA results of weight in tirzepatide 15 mg vs. insulin in the treatment of type 2 diabetes.

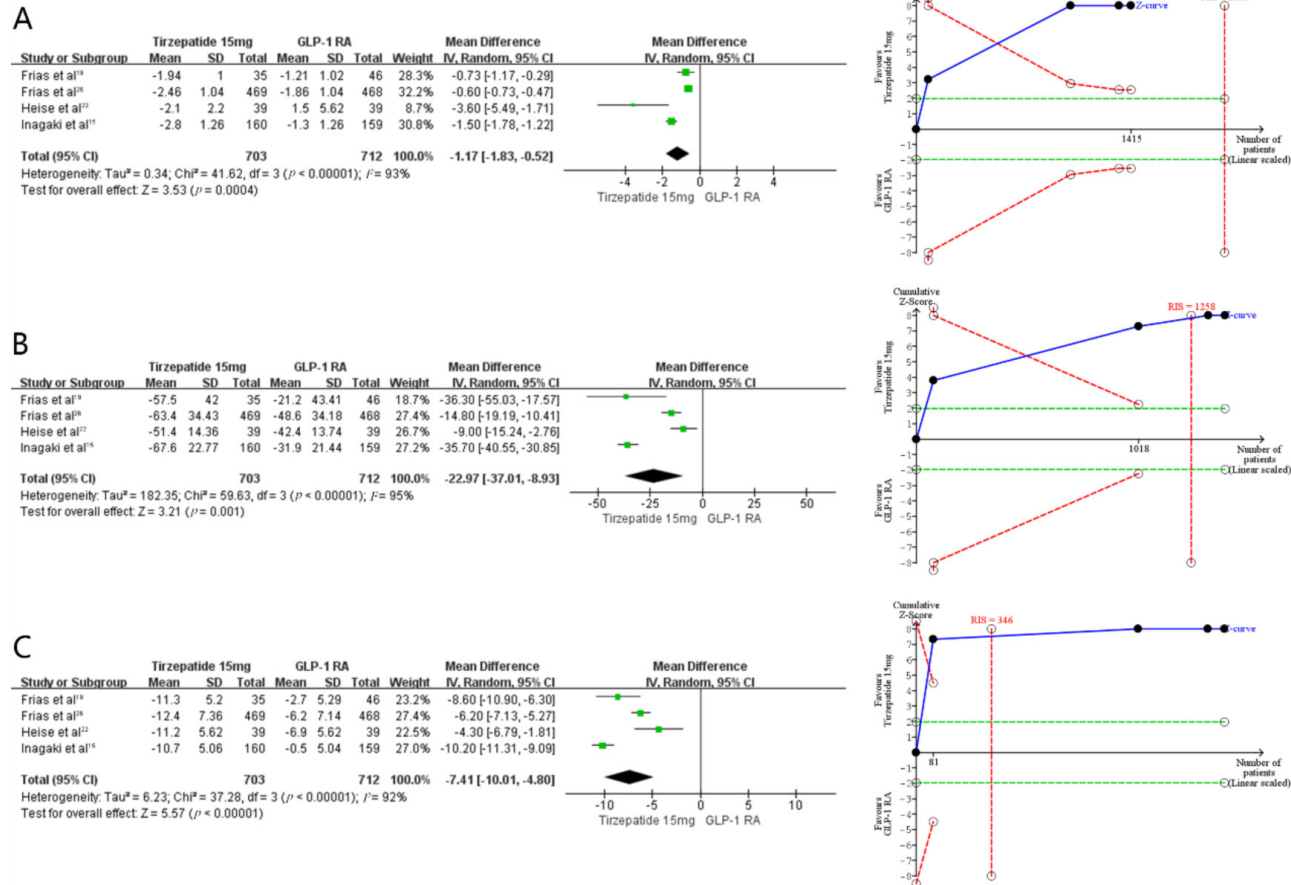


Figure 5. Meta-analysis and TSA results of efficacy endpoint in tirzepatide 15 mg vs. GLP-1 RA in treating type 2 diabetes. **A**, Meta-analysis and TSA results of HbA1c in tirzepatide 15 mg vs. GLP-1 RA in the treatment of type 2 diabetes. **B**, Meta-analysis and TSA results of FSG in tirzepatide 15 mg vs. GLP-1 RA in the treatment of type 2 diabetes. **C**, Meta-analysis and TSA results of weight in tirzepatide 15 mg vs. GLP-1 RA in the treatment of type 2 diabetes.

re conclusive, while the total AEs and serious AEs were inconclusive (Table II).

Tirzepatide 15 mg vs. GLP-1 RA

Four studies^{15,19,22,26} were included to compare the safety endpoints of “tirzepatide 15 mg vs. GLP-1 RA”. Meta-analysis revealed that, compared with the GLP-1 RA, hypoglycemia (<54 mg/dl) (RR 4.19, 95% CI 1.06-16.56, $p=0.04$) in tirzepatide 15 mg was dramatically higher, while the total AEs (RR 1.05, 95% CI 0.97-1.13, $p=0.20$), serious AEs (RR 1.06, 95% CI 0.41-2.76, $p=0.90$) and GI AEs (RR 1.43, 95% CI 0.87-2.34, $p=0.15$) were comparable. TSA showed that the results obtained from the current amount of information need more research and demonstration. Sensitivity analysis showed that the combined sensitivity of serious AEs was low, and the result was robust. The combined sensitivity of total AEs was high, and the result was labile, and the sensitivity analysis showed that the heterogeneity of total AEs was derived from Heise et al²². When the study of Heise et al²² was excluded from the total AEs, the heterogeneity disappeared, and the combined results suggested that the total AEs of tirzepatide 15 mg were significantly higher than that of GLP-1 RA (RR 1.09 95 CI% 1.02-1.16, $p=0.01$) (Table II). The comparison of each outcome for tirzepatide 15 mg vs. placebo, insulin, and GLP-1RA is shown in Figure 6.

Publication Bias Assessment

The funnel plot revealed the basic symmetry of the scatter on both sides. In addition, the Harbord regression of total AEs showed no evident publication bias ($p=0.618$) (Figure 7).

Discussion

A total of 9 clinical trials and 4,148 sample sizes were included in this meta-analysis and TSA, making it the publication with the largest sample size on tirzepatide 15 mg for type 2 diabetes. These studies are made more reliable and comprehensive by TSA. These analyses confirmed the efficacy and safety of tirzepatide while comparing 3 different treatment regimens.

Meta-analysis demonstrated that tirzepatide 15 mg was significantly more effective than placebo in reducing HbA1c, FSG, and body weight. Moreover, TSA revealed that the current results were conclusive, suggesting a definite hypoglycemic

effect of tirzepatide 15 mg. When compared to insulin, a 15 mg dose of tirzepatide showed a significant decrease in HbA1c, FSG, and weight. The TSA analysis confirmed that tirzepatide provided a clear advantage over insulin in terms of its hypoglycemic effect. HbA1c, FSG, and weight were significantly lower in tirzepatide 15 mg than in GLP-1 RA. TSA indicated definitive evidence for the current results. This evidence suggests that tirzepatide 15 mg has a more potent hypoglycemic effect than GLP-1 RA, which may be associated with insulin sensitization in patients. The GIP receptor (GIPR) activation by tirzepatide is stronger than that of conventional GLP-1 receptor (GLP-1R)^{27,28}. GLP-1 and GIP have a role in promoting insulin secretion and inhibiting glucagon levels in hyperglycemic states^{7,26}. The specific hypoglycemic mechanism of tirzepatide can have two aspects. On the one hand, tirzepatide improves insulin sensitivity by activating GLP-1R to enhance pancreatic β -cells function²⁹, delay gastric emptying³⁰, and reduce weight. On the other hand, tirzepatide can also improve systemic insulin sensitivity by inducing metabolic pathways associated with glucose, lipid, and BCAA oxidation in a weight-dependent and non-weight-dependent manner. Furthermore, the efficiency of weight-independent insulin sensitization is achieved by activating the GIPR³¹. Frias et al¹⁹ found that tirzepatide consistently reduced HbA1c, while Rosenstock et al²¹ discovered that HbA1c gradually plateaued in the tirzepatide-treated group. Guidelines¹⁸ stated that HbA1c $<5.7\%$ was considered normoglycemic, and our study observed that tirzepatide normalized HbA1c in more patients with type 2 diabetes. Continuous glucose monitor (CGM) and self-monitored blood glucose (SMBG) enable physicians to understand the patient's glycemic status, thus helping patients to better control their glycemic status^{32,33}. Ludvik et al²⁵ found that the use of tirzepatide resulted in a significant improvement in the levels monitored by SMBG and a significant reduction in patients' glycemic 2 hours postprandial. Moreover, they also stated that delayed gastric emptying was not a key driver of tirzepatide-induced postprandial glycemic efficacy. Battelino et al³⁴ reported that tirzepatide could significantly lower glycemic without increasing the risk of hypoglycemia in the presence of CGM monitoring of glycemic.

Weight loss is also one of the major benefits of tirzepatide in type 2 diabetes. Meta-analysis revealed that tirzepatide 15 mg was significantly more effective for weight loss than placebo, insu-

	HbA1c	FSG	Weight	Total AEs	Serious AEs	GIAEs	MACE-4	Hypoglycaemia ($<54\text{mg/dl}$)
TZP 15mg vs. Placebo	-1.88	-51.46	-9.73	1.22	0.72	3.59		1.06
TZP 15mg vs. Insulin	-1.09	-5.91	-14.36	1.24	0.83		0.51	0.39
TZP 15mg vs. GLP-1 RA	-1.17	-22.97	-7.41	1.05	1.06	1.43		4.19

Figure 6. Comparison of each outcome for tirzepatide 15 mg vs. placebo, insulin, and GLP-1RA. Green means $p < 0.05$ and the difference is positive. Red means $p < 0.05$ and the difference is negative. Yellow means $p > 0.05$. The values in the table are RR/MD.

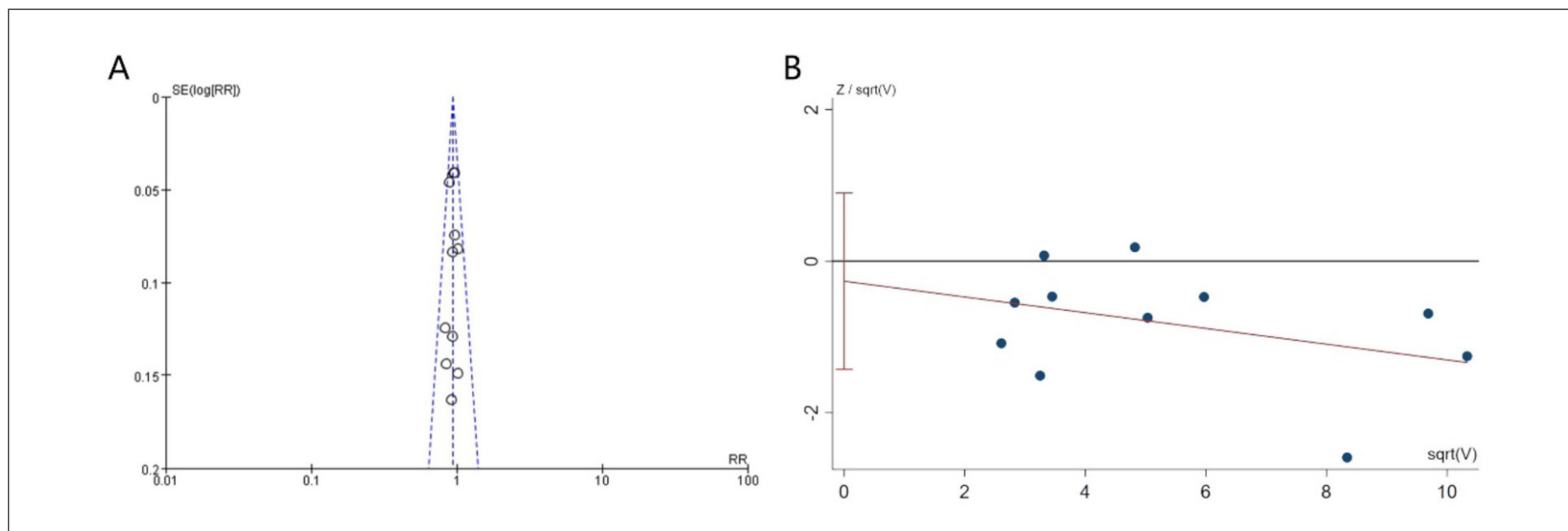


Figure 7. Publication bias assessment graph. **A**, Funnel plot. **B**, Harbord regression.

lin, and GLP-1 RA. TSA indicated that the current results were conclusive, suggesting that tirzepatide has a definite weight loss effect, an additional benefit of tirzepatide *vs.* insulin, and GLP-1 RA. The significant weight loss effect of tirzepatide contributes to improved glycemic control for patients with type 2 diabetes, and the additional weight loss may provide higher protection for those patients. The weight loss effect of tirzepatide is dependent on the activation of GLP-1R and GIPR. GLP-1 inhibits appetite and food intake by slowing gastric emptying, promoting satiety⁷, and activating anorexia pathways in the brain³⁵, which leads to weight loss. GIP, on the other hand, can effectively suppress food intake by directly activating hypothalamic GIPR³⁶. The combination of GIP and GLP-1 showed powerful effects on weight loss, independent of insulin sensitivity and lipid metabolism³⁷. For example, in diet-induced obese mice, the combination of GIP and GLP-1 displayed more significant anorexic effects by enhancing satiety, reducing the intake of high-fat diets, and reducing their preference for sweet taste³⁸. Weight loss can help increase insulin sensitivity²¹ and reduce cardiovascular risk, among others²⁴. In addition, Del et al²⁴ first showed that the benefits of tirzepatide on glycemic and weight lasted for more than 1 year without an increased risk of MACE-4. These pieces of evidence point to tirzepatide aiding in weight loss, increasing insulin sensitivity, and lowering the risk of cardiovascular disease in type 2 diabetes patients.

The total AEs and GI AEs of tirzepatide 15 mg were dramatically higher for safety endpoints than placebo. This means that tirzepatide 15 mg has certain AEs, and GI AEs are its major AEs, while tirzepatide 15 mg will not increase the serious AEs and hypoglycemia. The total AEs were significantly higher for tirzepatide 15 mg compared to insulin. Neither of the two included studies^{24,25} reported rates of GI AEs, but they both reported an increase in individual GI AEs such as nausea, vomiting, and constipation. Hence, GI AEs remain the central contradiction of tirzepatide, which is the main reason for the higher rate of total AEs of tirzepatide than insulin. Mild to moderate GI AEs are the most common AEs of tirzepatide (vomiting, nausea, decreased appetite, diarrhea, abdominal distension, etc.)³⁹. Ludvik et al²⁵ discovered that the gastrointestinal adverse reactions caused by tirzepatide were more pronounced at the beginning of treatment. However, the gastrointestinal symptom response gradually decreased over time. The mechanism of tirzepati-

de-induced gastrointestinal adverse reactions had not been fully elucidated. Nausea and vomiting are one of the main reasons patients stop treatment prematurely¹⁹, and its mechanism may be related to the activation of GLP-1R in the central nervous system⁴⁰. The occurrence of diarrhea and abdominal distension may be related to the change in lower digestive tract transport rate, but there is still a lack of evidence to support it. The stable glycemic regulatory ability of tirzepatide originates from the properties of GLP-1 and GIP. GLP-1 inhibits glucagon secretion under hyperglycemic and normoglycemic conditions⁷ and has no inhibitory effect under hypoglycemic conditions. GIP stimulates insulin release under hyperglycemic conditions and elevates glucagon levels under normoglycemic or hypoglycemic conditions²⁶, thereby reducing the occurrence of hypoglycemia. The meta-analysis and TSA revealed that MACE-4 and hypoglycemia were significantly lower with tirzepatide 15 mg than with insulin, implying that higher doses of tirzepatide had a lower risk of cardiovascular and cardiovascular risk hypoglycemia with insulin. However, the lack of comparative studies of MACE with tirzepatide *vs.* placebo makes it unclear how well tirzepatide improves cardiovascular prognosis. The total AEs, serious AEs, and GI AEs were equal in tirzepatide 15 mg compared with GLP-1 RA, which indicates that tirzepatide 15 mg will not increase these significant AEs. Sensitivity analysis showed that the heterogeneity of total AEs with tirzepatide 15 mg compared to GLP-1 RA was derived from Heise et al²², indeed it disappeared after the exclusion of this study, and the combined results suggested that total AEs with tirzepatide 15 mg was significantly higher than that with GLP-1 RA (RR 1.09 95 CI% 1.02-1.16, $p=0.01$). Total AEs of tirzepatide 15 mg and GLP-1 AR in the study of Heise et al²² were 43/45 and 43/44, respectively, which were very close to each other. The reason may be that the sample size of this study is too small to reflect the differences between groups, which leads to the formation of heterogeneity. After removing this study, the combined results suggested a higher risk for tirzepatide 15 mg on total AEs. Therefore, contrary to previous opinion¹⁶, we believe that the total AEs of tirzepatide 15 mg are significantly higher than that of GLP-1 RA. However, since the cumulative sample size has not yet reached the expected informative value, this result needs to be proven by more relevant results. Interestingly, compared with GLP-1 RA, the hypoglycemia of tirzepatide 15

mg was increased remarkably. Only Frías et al²⁶ and Inagaki et al¹⁵ were included in this meta-analysis, whereas Frías et al²⁶ accounted for 80% of the analysis, while Inagaki et al¹⁵ accounted for only 20%. It means that the results were mainly dominated by Frías et al²⁶, and TSA indicated that this result was inconclusive. Therefore, it is controversial that the hypoglycemia of tirzepatide 15 mg is higher than GLP-1 RA, which needs to be further demonstrated by more related studies. In addition, the current related studies reported that tirzepatide 15 mg did not induce severe hypoglycemia^{41,42}, which meant that tirzepatide 15 mg was still a relatively safe strategy.

Although our study strictly followed the PRISMA guidelines for systematic reviews and meta-analysis methods, the study still has limitations (as shown below). 1) Del et al²⁴, Ludvik et al²⁵, and Frías et al²⁶ were open-label studies with a high risk of implementation bias, which would reduce the confidence of the results. 2) Narrow inclusion criteria limited the readability of the results. Frías et al¹⁹ included only patients with HbA1c of 7.0 to 10.5% and BMI of 23-50 kg/m². Ludvik et al²⁵ subjectively excluded subjects with pancreatitis, proliferative diabetic retinopathy, and renal dysfunction. Also, each study had European-American and Asian ethnicity as the primary study population. These factors may have caused the results to be less generalizable. 3) The available studies only reported the MACE of “tirzepatide vs. insulin”, while the cardiovascular prognostic impact of tirzepatide compared to placebo or GLP-1 RA remains unclear. Clinical studies in the future could focus on exploring the effects of tirzepatide on lipids, blood pressure, and MACE. 4) Data on short-term follow-up are lacking. Although long-term efficacy is the crucial measure of the effectiveness of tirzepatide treatment, the psychological desire of patients with type 2 diabetes to lower their glycemic levels dictates that short-term efficacy is also essential. Regrettably, the majority of the data regarding efficacy were obtained for long-term outcomes, with fewer studies^{20,43} available for short-term efficacy assessment and comparison.

As a novel dual-receptor agonist, tirzepatide has a significant effect in reducing blood glucose. However, because of the existing studies' limitations, we hope the relevant studies will be further improved. First, future clinical trials could be conducted in a stratified study. The effects of tirzepatide 15 mg on patients with type 2 diabetes of different ages, course of the disease, gender,

and basal weight will be investigated by controlling for relevant variables, thus comprehensively evaluating the characteristics of drug effects on different baseline populations. Secondly, compared with insulin, tirzepatide 15 mg showed the effect of reducing MACE-4. A study by Wilson et al⁴⁴ also showed that tirzepatide could reduce the levels of inflammatory markers hs-CRP, YKL-40, and endothelial dysfunction marker ICAM-1 in a dose-dependent manner. This evidence suggested that high doses of tirzepatide might have significant cardiovascular protective effects. Therefore, future studies can be devoted to exploring the value of tirzepatide in cardiovascular risk reduction. Thirdly, previous studies^{25,45,46} showed that tirzepatide reduced triglyceride, very low-density lipoprotein, apolipoprotein, and apolipoprotein III and increased high-density lipoprotein levels in addition to lowering blood glucose and weight. Moreover, Ludvik et al²⁵ showed that tirzepatide had the additional benefit of reducing mean systolic and diastolic blood pressure. However, there is no large randomized, double-blind trial sample to verify the role of tirzepatide in regulating blood lipids and lowering blood pressure, which may be the entry point of future research. Tirzepatide administration significantly improves the daily life of individuals with type 2 diabetes and can also provide relief for those dependent on insulin. We look forward to the continued promotion of tirzepatide-related clinical trials, and hope that it will positively impact patients suffering from type 2 diabetes.

Conclusions

Tirzepatide 15 mg has excellent hypoglycemic and weight loss effects superior to insulin and GLP-1 RA. GI AEs are the major AEs for tirzepatide 15 mg, significantly higher than placebo and insulin and comparable to GLP-1 RA. Tirzepatide 15 mg can also reduce the risk of hypoglycemia and cardiovascular risk relative to insulin. Ultimately, tirzepatide 15 mg is a better therapeutic strategy for type 2 diabetes. However, its GI AEs must be investigated.

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Authors' Contributions

Xinyu Yang participated in the study conception and design.

Xinyu Yang, Shuang Yin, and Yunfeng Yu conducted database research. Gang Hu and Yunfeng Yu performed the statistical analysis. Xinyu Yang and Gang Hu wrote the first draft of the manuscript. Shuang Yin, Yunfeng Yu, Fei Zhang, Manli Zhou, and Weixiong Jian wrote parts of the manuscript. Weixiong Jian reviewed and revised the manuscript. Pei Liu assisted in adjusting the direction and framework of the study and performed statistical tests and revised language expressions. All authors contributed to the revision of the manuscript and read and approved the submitted version.

Conflicts of Interest

The authors hereby state that the study has no conflict of interest.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

Availability of Data and Materials

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

ORCID ID

X.-Y. Yang: 0000-0001-6124-9166

S. Yin: 0000-0001-9007-6962

Y.-F. Yu: 0000-0002-7309-5608

G. Hu: 0000-0002-6252-0082

F. Zhang: 0000-0002-4246-5397

M.-L. Zhou: 0000-0001-8404-1341

P. Liu: 0000-0002-4897-2736

W.-X. Jian: 0000-0002-6197-4787

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