ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

A network meta-analysis of the effectiveness and safety of different doses of ertugliflozin in the treatment of type 2 diabetes

Zhao Qian[1], Sang Yafei[1], Shang Lijing[1], Ma Yujin[2*]

[1]College of Clinical Medicine of Henan University of Science and Technology, Luoyang, 471003, China
[2]Department of Endocrinology and MeTableolism, the First Affiliated Hospital of Henan University of Science and Technology, Luoyang, 471003, China
**Corresponding Author*

Abstract: *Objective: To conduct a network meta-analysis to systematically evaluate the efficacy and safety of different doses of ertugliflozin in the treatment of Type 2 diabetes. Methods: The Pubmed, Embase, Cochrane library, CNKI, Wanfang, Weipu, CBM, Web of science and other daTableases were searched by computer from the beginning of the daTablease to 2021. To search for randomized controlled trial of different doses of ertugliflozin in the treatment of type 2 diabetes, to screen the literature according to inclusion and exclusion criteria, to extract data, and to evaluate the quality of the included studies by Cochrane systematic evaluation methods,using RevMan5.3 software and Stata 16.0 versions for analysis. RESULTS: A total of 11 randomized controlled trials (RCTs) were enrolled, including 5713 patients, The results of network meta-analysis showed that ertugliflozin 5,10,15,25 mg were superior to placebo in reducing glycosylated hemoglobin, Only 15 mg was statistically significant($p<0.05$),and ertugliflozin 15 mg ranked first in the rank probability chart; 5,10,15 and 25 mg of ertugliflozin could reduce the fasting plasma glucose (FPG) in patients with type 2 diabetes Mellitus (T2D),and all had statistical significance($p<0.05$),in the rank probability chart, ertugliflozin 10mg ranks first; Compared with the Placebo Group, ertugliflozin 5,10,15 and 25 mg reduced the weight of the patients, which was statistically significant($p<0.05$). Ertugliflozin 10 mg ranked first in the rank probability chart; In the incidence of adverse drug reactions, hypoglycemia and discontinuation due to adverse drug reactions,compared with the placebo group, only 5 mg and 15 mg group had statistical significance($p<0.05$), the difference was significant; The incidence of adverse drug reactions in ertugliflozin 15mg group was lower than that in 5mg group and the incidence of hypoglycemia was higher than that in 5mg group;The discontinuation rate of ertugliflozin 5mg group was higher than that in 15mg group,the difference was significant. But limited by the quality of the study, there is publication bias, and the conclusion still needs to be further verified by high-quality studies. Conclusion: The different dose groups of ertugliflozin are effective for the treatment of T2DM. 15 mg of ertugliflozin can significantly improve HbA1c, while the effect of 10 mg on FPG and body weight is more significant. But there are still certain security issues. Due to the limited quality of relevant literature, there is publication bias, and some dose-related literature is less included, and more large-sample, multi-center high-quality literature is still needed for verification.*

Keywords: *Ertugliflozin; type 2 diabetes mellitus; efficacy; safety; network meta-analysis*

1. Introduction

There are more than 422 million people living with diabetes in the world, 90-95% of them suffer from Type 2 diabetes (T2D) [1]. Although the blood sugar control of this population has improved, many T2D patients have not achieved their blood sugar control goals [2]. Diabetes patients urgently need safe and effective new oral hypoglycemic drugs. There are currently a variety of oral and injectable drugs that can be used as a single or combination therapy for T2D patients. The choice of drugs is driven by many factors, including the ability to reduce glycosylated hemoglobin (HbA1c), side effects, cost, risk of hypoglycemia, patient preference and reduction The ability of cardiovascular disease risk [3]. In the treatment process, joint decision-making and individualization of drug treatment should be emphasized, and efforts should be made to strengthen treatment in a timely and purposeful manner.

Sodium-glucose transport-2 proteins (SGLT2) inhibitors are a new class of diabetes treatment drugs

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

that inhibit the absorption of glucose in the proximal convoluted tubules of the kidney, increase the excretion of urine sugar, and thereby reduce blood sugar levels. Long-term use can reduce HbA1c levels and reduce the toxicity of hyperglycemia in the body [3-4]. This category of therapeutic drugs currently includes four drugs approved in the United States and Europe: canagliflozin, dapagliflozin, empagliflozin, and the latest ertugliflozin. Ertugliflozin was approved by the U.S. Food and Drug Administration (FDA) in December 2017 and approved by the European Medicines Agency in January 2018. It is the fourth SGLT2 inhibitor approved for the treatment of T2D. This product alone or in combination with other oral hypoglycemic agents has a good effect in reducing HAblc, body weight, and fasting blood glucose. Ertugliflozin is a film-coated Tablelet with 2 dosage specifications of 5mg and 15mg. The FDA recommends that the initial dose of ertugliflozin for T2D patients is 5mg qd. If the drug is tolerated and additional blood glucose control is required, It can be increased to 15 mg qd, but the best recommended dose has not been proposed. This study collects relevant evidence, discusses the difference in the efficacy of different doses of ertugliflozin in the treatment of type 2 diabetes from the perspective of evidence-based medicine, and finds the best dose in order to provide evidence for clinical rational drug use.

2. Materials and methods

2.1 Study registration

The design of the present study adheres to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA-P) statement, and it is registered in OSF(https://osf.io/)with https://osf.io/w8p4v/.

2.2 Literature search strategy

A computer search of eight daTableases, Pubmed, Embase, Cochrane Library, CNKI, Wanfang, Weipu, CBM, and Web of Science, was a randomized controlled study of Ertugliflozin in the treatment of T2DM. The search time was from the esTablelishment of the daTablease to April 2021. The search is carried out by combining subject words and free words, and the language is limited to Chinese and English. Take "type 2 diabetes "," non-insulin-dependent diabetes "," non-insulin-dependent diabetes "," ertugliflozin "," ertugliflozin "," ertugliflozin "," random control" and "random" as Chinese search terms; "D iabetes M ellitus type 2""type 2diabetes""type 2diabetes mellitus""Diabetes Mellitus, Noninsulin-Dependent ""Non insulin dependent diabetes mellitus"" NIDDM" “ertugliflozin” ""5-(4-chloro-3-(4-ethoxybenzyl)-1-hydroxymethyl-6, 8-dioxabicyclo(3.2.1)octane-2, 3, 4-triol ""Steglatro"" PF 04971729"" PF04971729"" PF-04971729"" randomized ""randomized controlled trial "and so on are English key words; At the same time, trace back the references of the included literature to ensure the comprehensiveness of the search..

2.3 Documentation inclusion and exclusion criteria

2.3.1 Documentation inclusion criteria

According to the PICO criteria, the inclusion criteria of this study were formulated from four aspects: Participant, Intervention, Control, Outcome, and strictly referred to the implementation.

Inclusion criteria: 1. Research type: Randomized Controlled Trials (RCT) published at home and abroad, and the language is limited to English and Chinese. The same study is included in the most complete report. 2. The research subjects are patients with type 2 diabetes, and the diagnostic criteria are based on the American Diabetes Association (ADA) standards [6]. 3. Intervention measures The experimental group is the ertugliflozin treatment group, and the control group is the placebo group. Both groups can be treated with other hypoglycemic drugs on the basis of the intervention measures, and the treatment time is ≥12 weeks. 4. Outcome indicators Effective indicators include: (1) glycosylated hemoglobin (HbA1c) (%); (2) fasting blood glucose (FPG) (mmol/L); (3) body weight.

Safety indicators include: (1) hypoglycemia; (2) adverse drug-related reactions (harmful reactions that are not related to the purpose of medication when using ertugliflozin: gastrointestinal diseases, neurological diseases, Cardiovascular diseases and urinary diseases, etc., adverse reactions identified by the researchers).

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

2.3.2 Exclusion criteria

Exclusion criteria (1) non-RCT studies; (2) moderate to severe cardiac or renal insufficiency; (3) repeated publications; (4) data cannot be used for software analysis; (5) languages other than Chinese and English.

2.4 Screening of literature and data extraction

Two researchers read the title and abstract of the literature independently, screen out the obvious irrelevant review or pharmacological test, and read the full text if it is a randomized controlled trial to determine whether it meets the inclusion criteria.If there is disagreement, it is determined by discussion or consultation with a third party. The basic characteristics of the included study mainly included the number of first authors, the number of experimental and control groups, the average age, the glycosylated hemoglobin value (HbA1c), the fasting blood glucose value (FPG), the body weight, the intervention measures and the outcome index.

2.5 Quality evaluation of studies included

Two investigators evaluated the risk of bias in the included studies in accordance with the quality evaluation criteria recommended in 5.3 of the Cochrane Evaluation Manual. For each included literature, the random sequence was generated, hidden grouping, blinded to the investigator's enrolled patients, and the evaluation Whether the result report is complete, reporting bias, and other biases [7] make "low risk" (meaning complete literature and high credibility), "high risk" (meaning unclear literature and low credibility) and "Unclear" (indicating that the literature information is unclear and the bias is uncertain) judgment.

2.6 Statistical methods

All results are evaluated by the 95% confidence interval (95% CI) obtained by the weighted mean difference (MD) [8]. In addition, using Stata 16.0 software to draw a network diagram, each node represents a certain intervention, the size of the node represents the sample size, and the thickness of the line represents the number of studies included in the study. Each parameter was analyzed by network meta-analysis, different intervention measures were compared, and analyzed based on non-informative test to achieve accuracy and effect. Data analysis and bias risk assessment were carried out using Stata 16.0, and the intervention measures were sorted using a graded probability map.

3. Results

3.1 Literature search results

412 first-checked articles [the daTablease and the number of checked-out articles are as follows: PubMed(n=25), Cochrane(n=117), Embase(n=175), CNKI(n=6), Wanfang(n=1), VIP (n=6), CBM (n=6), Web of science (n=76)], remove the weight, read the title and abstract, read the full text further, and finally included 11 RCT studies [9-19], the literature screening process is shown in Figure 1. The included literatures are all double-blind and multi-center randomized controlled trials, with a total of 5713 patients, and all publications are in English.

These studies were published from 2015 to 2021, and the trial period were 12 to 52 weeks. Intervention measures include ertugliflozin 5, 10, 15, 25 mg. The basic characteristics of the included literature and Cochrane system bias assessment are shown in Table 1 and Figure 2; The mesh evidence of the main parameters is shown in Figure 3.

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

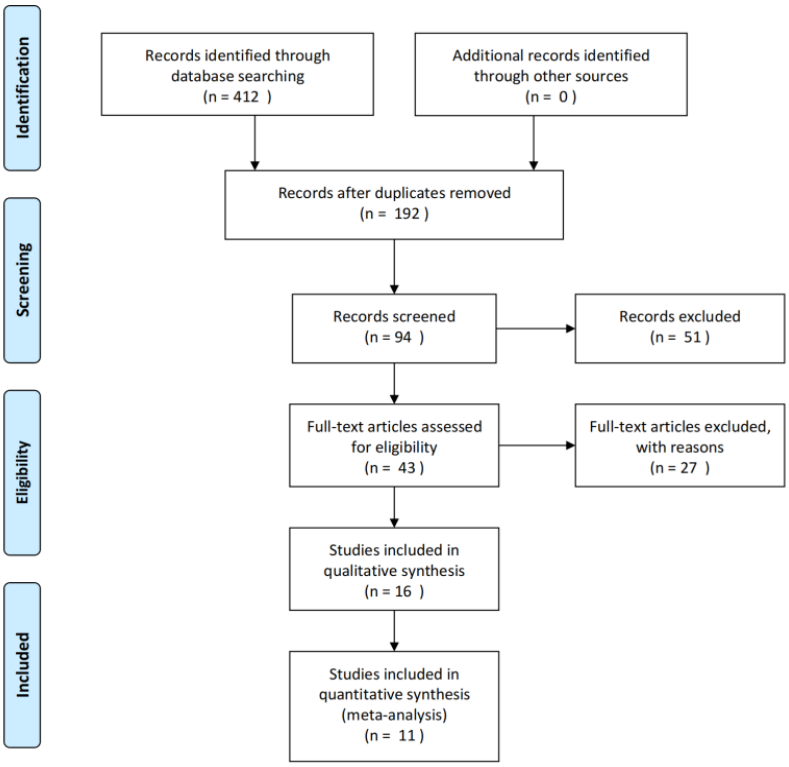
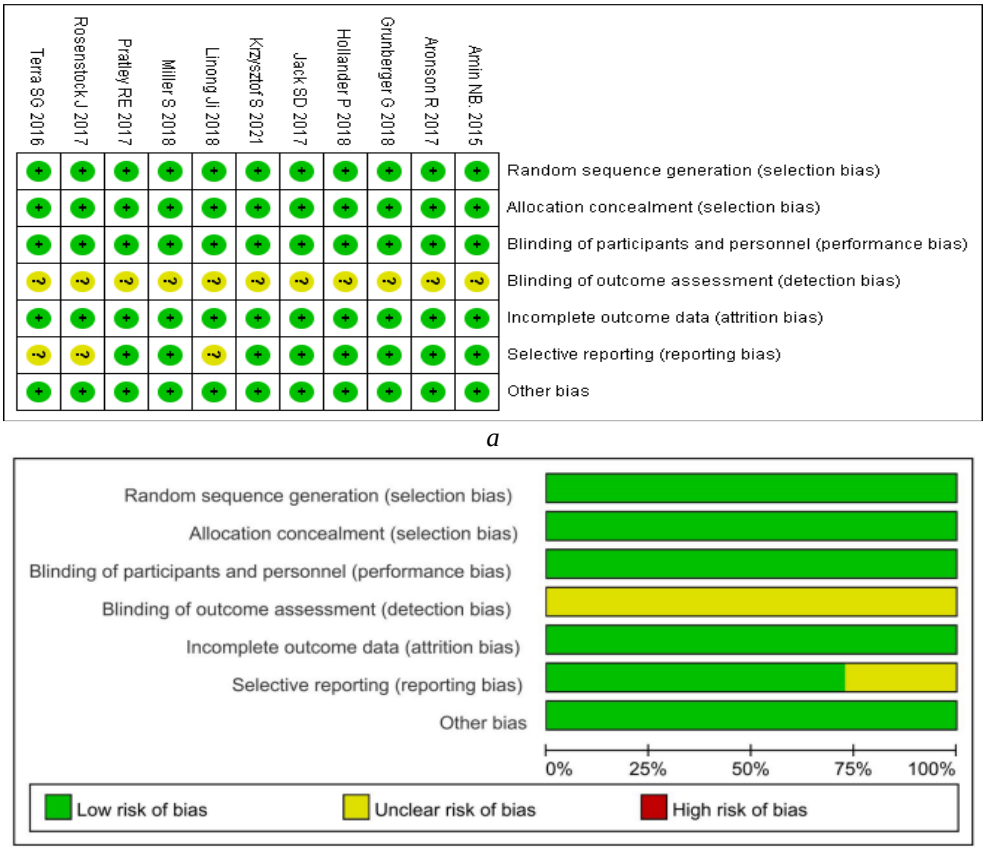


Figure.1 Flow chart of the literature screening



a

b

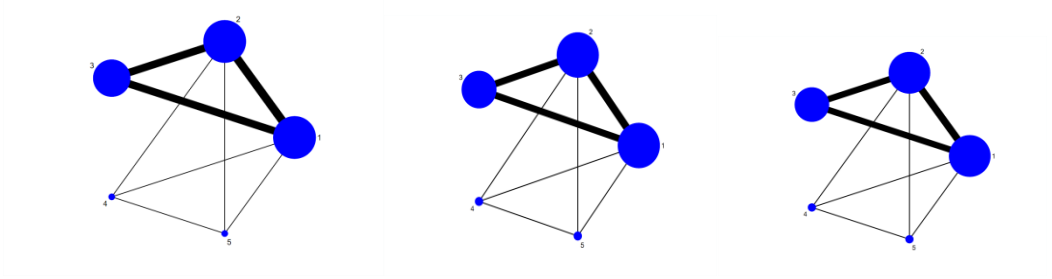
Figure.2 Evaluation on the methodological quality of the included studies

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

Table.1 Basic characteristics of the included studies

Included literature	Intervention	Number of patients (n)	Age	Course of disease (years)	HbA1C baseline level (%)	FPG baseline level (mmol/L)	体重 (KG)	BMI (Kg/m²) baseline level	Background treatment	Treatment cycle
Samuel	PBO	153	58.3 (9.2)	9.4 (5.6)	8.0 (0.9)	9.4 (2.1)	86.4 (20.8)	30.3 (6.4)	metformin+ sitagliptin	26/52
Dagogo-Jack[9]	ERTU 5mg po qd	156	59.2 (9.3)	9.9 (6.1)	8.1 (0.9)	9.3 (2.1)	87.6 (18.6)	31.2 (5.5)		
NCT02036515	ERTU 15mg po qd	153	59.7 (8.6)	9.2 (5.3)	8.0 (0.8)	9.5 (2.2)	86.6 (19.5)	30.9 (6.1)		
Linong Ji[10] NCT02630706	PBO	167	56.9 (9.0)	6.4 (5.1)	8.1 (1.0)	9.2 (2.1)	70.1 (12.4)	26.1 (3.4)	metformin	26
	ERTU 5mg po qd	170	56.1 (9.0)	7.0 (5.0)	8.1 (0.9)	9.5 (2.0)	71.4 (11.1)	26.0 (2.8)		
	ERTU 15mg po qd	169	56.3 (9.3)	7.5 (5.1)	8.1 (0.9)	9.3 (2.3)	69.5 (10.9)	25.7 (3.2)		
Terra, S. G[11] NCT01958671	PBO	153	56.1 (10.9)	4.63(4.52)	8.11 (0.92)	10.0 (2.5)	94.2 (25.2)	33.3 (6.8)	Not sure	26
	ERTU 5mg po qd	156	56.8 (11.4)	5.11(5.09)	8.16 (0.88)	10.0 (2.7)	94.0 (25.4)	33.2 (7.4)		
	ERTU 15mg po qd	152	56.2 (10.8)	5.22(5.55)	8.35 (1.12)	9.9 (2.7)	90.6 (18.3)	32.5 (5.7)		
N. B. Amin[12] NCT01059825	PBO	54	54.0±8.1	6.4(0.3-20)	8.08±0.14	9.18±0.31	/	30.6±0.61	metformin	12
	ERTU 5mg po qd	55	54.7±7.7	6.7(0.3-30)	7.88±0.13	8.69±0.32		31.1±0.85		
	ERTU 10mg po qd	55	57.3±6.5	6.1(0.2-20)	8.13±0.17	9.07±0.35		30.7±0.80		
	ERTU 25mg po qd	55	54.2±8.8	6.0(0.3-18)	8.30±0.16	9.52±0.43		29.8±0.67		
Strojek, Krzysztof[13] NCT01986881	PBO	48	64.4 (9.3)	8.1 (6.9)	8.2 (1.2)	9.8 (3.2)	90.0 (21.2)	30.8 (5.7)	Not sure	18
	ERTU 5mg po qd	55	64.9 (8.7)	8.7 (6.8)	8.3 (1.0)	9.6 (2.6)	85.8 (14.7)	30.0 (4.8)		
	ERTU 15mg po qd	54	64.3 (9.0)	8.6 (5.9)	8.4 (1.0)	10.2 (2.4)	87.5 (21.2)	31.4 (5.9)		
Julio Rosenstock[14] NCT02033889	PBO	209	56.5±8.7	8.0±6.3	8.2±0.9	9.4±2.3	84.5 ± 17.1	30.7±4.7	metformin	26
	ERTU 5mg po qd	207	56.6±8.1	7.9±6.1	8.1±0.9	9.3±2.5	84.8 ±17.2	30.8±4.8		
	ERTU 15mg po qd	205	56.9±9.4	8.1±5.5	8.1±0.9	9.3±2.5	85.3 ±16.5	31.1±4.5		
Sam Miller[15] NCT02226003	PBO	97	54.3 (10.3)	6.8 (6.5)	9.0 (0.9)	11.5 (2.5)	95.0 (20.5)	32.7 (6.2)	sitagliptin	26
	ERTU 5mg po qd	98	56.4 (9.3)	5.7 (5.0)	8.9 (0.9)	11.0 (2.6)	90.8 (20.7)	32.0 (6.3)		
	ERTU 15mg po qd	96	56.1 (10.1)	6.5 (6.5)	9.0 (0.9)	10.4 (2.6)	91.2 (22.5)	32.1 (5.8)		
Priscilla Hollander[16] NCT01999218	PBO	437	57.8 ± 9.2	7.5 ± 5.6	(7.8±0.6)	8.8±1.9	86.8 ± 20.7	31.2±6.4	Glimepiride	52
	ERTU 5mg po qd	448	58.8 ± 9.7	7.4 ± 5.7	(7.8±0.6)	9.0±1.9	87.9 ± 18.9	31.7±5.5		
	ERTU 15mg po qd	440	58.0 ± 9.9	7.5 ± 5.7	(7.8±0.6)	9.1±2.0	85.6 ± 19.1	31.3±6.2		
George Grunberger[17] NCT01986855	PBO	154	67.5 (8.9)	13.1 (8.1)	8.1 (0.9)	8.71 (3.13)	90.4 (18.9)	33.2 (6.1)	Insulin + sulfonylureas	26/52
	ERTU 5mg po qd	158	66.7 (8.3)	14.9 (9.0)	8.2 (1.0)	8.94 (3.13)	89.4 (22.5)	32.6 (6.8)		
	ERTU 15mg po qd	155	67.5 (8.5)	14.5 (8.5)	8.2 (0.9)	8.75 (2.66)	85.8 (17.4)	31.7 (5.3)		
Richard E. Pratley[18] NCT02099110	PBO	247	54.8 (10.7)	6.2 (5.2)	8.5 (1.0)	9.86 (2.59)	89.8 (23.5)	31.7 (6.5)	sitagliptin	26/52
	ERTU 5mg po qd	250	55.1 (10.1)	7.1 (5.4)	8.6 (1.0)	10.23(2.9)	88.6 (22.2)	31.8 (6.2)		
	ERTU 15mg po qd	248	55.3 (9.5)	7.3 (5.4)	8.6 (1.0)	9.97(2.54)	88.0 (20.3)	31.5 (5.8)		
Ronnie Aronson[19] NCT01958671	PBO	153							metformin	26/52
	ERTU 5mg po qd	156	56.4 (11.0)	5.0 (5.1)	8.2 (1.0)	/	/	33.0(6.7)		
	ERTU 15mg po qd	152								

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407



(A)HbA1c *(B)FDP* *(C)Body weight*

Figure.3 Network evidence map:PBO=1; ERTU 5mg=2; ERTU 15mg=3; ERTU 10mg=4; ERTU 25mg=5

3.2 Network meta analysis results

3.2.1 Effectiveness

3.2.1.1 HbA1c level

11 studies[9-19]reported the changes in HbA1c levels after the treatment of type 2 diabetes with ertugliflozin. The improvement effect of each treatment group of Ertugliflozin (5,10,15,25 mg) on the HbA1c of T2DM patients was better than that of placebo group, only 15 groups had statistical significance($p<0.05$) and the difference was significant. The network analysis results are shown in Figure 4.

ERTU15mg	0.31 (-1.76,2.37)	0.42 (-1.65,2.48)	0.52 (-0.19,1.23)	0.91 (0.20,1.62)
-0.31 (-2.37,1.76)	ERTU25mg	0.11 (-2.17,2.39)	0.22 (-1.79,2.22)	0.60 (-1.40,2.61)
-0.42 (-2.48,1.65)	-0.11 (-2.39,2.17)	ERTU10mg	0.11 (-1.90,2.11)	0.49 (-1.51,2.50)
-0.52 (-1.23,0.19)	-0.22 (-2.22,1.79)	-0.11 (-2.11,1.90)	ERTU5mg	0.39 (-0.30,1.08)
-0.91 (-1.62,-0.20)	-0.60 (-2.61,1.40)	-0.49 (-2.50,1.51)	-0.39 (-1.08,0.30)	Placebo

Figure.4 Results of HbAlc network meta analysis

3.2.1.2 Fasting blood glucose levels

The improvement of FDP level was reported in all studies. The effect of FDP improvement in each treatment group was better than that in placebo group, which is statistically significant ($p<0.05$) and the difference was significant. And 10 mg was superior to the other treatment groups. There was no statistical difference between the groups.The results of the network analysis are shown in Figure 5.

ERTU10mg	0.12 (-1.25,1.49)	0.77 (-0.50,2.04)	0.92 (-0.29,2.13)	1.72 (0.51,2.93)
-0.12 (-1.49,1.25)	ERTU25mg	0.65 (-0.62,1.92)	0.80 (-0.41,2.01)	1.60 (0.39,2.81)
-0.77 (-2.04,0.50)	-0.65 (-1.92,0.62)	ERTU15mg	0.15 (-0.36,0.66)	0.95 (0.44,1.46)
-0.92 (-2.13,0.29)	-0.80 (-2.01,0.41)	-0.15 (-0.66,0.36)	ERTU5mg	0.80 (0.32,1.29)
-1.72 (-2.93,-0.51)	-1.60 (-2.81,-0.39)	-0.95 (-1.46,-0.44)	-0.80 (-1.29,-0.32)	Placebo

Figure.5 Results of FPG network meta analysis

3.2.1.3 Weight

Figure 6 results showed that all the treatment groups (5,10,15,25 mg) of ertugliflozin significantly reduced the weight of the patients compared with the placebo group, and the difference was statistically significant($p<0.05$). And 10 mg was superior to the other treatment groups. There was no statistical difference between the groups.

ERTU10mg	0.26 (-1.64,2.15)	0.24 (-1.81,2.29)	0.30 (-1.51,2.11)	2.25 (0.44,4.06)
-0.26 (-2.15,1.64)	ERTU15mg	-0.02 (-1.91,1.88)	0.04 (-0.72,0.81)	2.00 (1.23,2.76)
-0.24 (-2.29,1.81)	0.02 (-1.88,1.91)	ERTU25mg	0.06 (-1.75,1.87)	2.01 (0.20,3.82)
-0.30 (-2.11,1.51)	-0.04 (-0.81,0.72)	-0.06 (-1.87,1.75)	ERTU5mg	1.95 (1.23,2.68)
-2.25 (-4.06,-0.44)	-2.00 (-2.76,-1.23)	-2.01 (-3.82,-0.20)	-1.95 (-2.68,-1.23)	Placebo

Figure.6 Results of body weight network meta analysis

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

3.2.2 Safety

3.2.2.1 Drug-related adverse reactions

Drug-related adverse events (including gastrointestinal diseases, nervous system diseases, cardiovascular diseases and urinary system diseases) were reported in all treatment regimens, compared with placebo groups, the incidence of adverse reactions was higher in 5 mg and 15 mg groups in ertugliflozin group, which is statistically significant($p<0.05$) and the difference was significant. The incidence of adverse reactions in the 15 mg group was lower than that in the 5 mg group, and the difference was significant. There was no statistical difference between the other treatment options and the placebo control.

ERTU15mg	0.11 (-0.91,1.14)	0.34 (-0.65,1.34)	0.08 (-0.18,0.33)	-0.24 (-0.50,0.03)
-0.11 (-1.14,0.91)	ERTU25mg	0.23 (-0.88,1.34)	-0.04 (-1.05,0.97)	-0.35 (-1.36,0.66)
-0.34 (-1.34,0.65)	-0.23 (-1.34,0.88)	ERTU10mg	-0.27 (-1.24,0.71)	-0.58 (-1.56,0.40)
-0.08 (-0.33,0.18)	0.04 (-0.97,1.05)	0.27 (-0.71,1.24)	ERTU5mg	-0.31 (-0.57,-0.06)
0.24 (-0.03,0.50)	0.35 (-0.66,1.36)	0.58 (-0.40,1.56)	0.31 (0.06,0.57)	Placebo

Figure.7 Results of drug-related adverse reactions network meta analysis

3.2.2.2 Hypoglycemic event

All treatment regimens reported hypoglycemia events. Only the 5 mg and 15 mg ertugliflozin group compared with the placebo group were statistically significant ($p<0.05$), and the difference was significant. Moreover, the incidence of hypoglycemia in the 5 mg group was lower than that in the 15 mg group, and the difference was significant. There was no statistical difference between the other treatment options and the placebo control.

ERTU10mg	0.00 (-2.65,2.65)	0.47 (-1.82,2.75)	0.59 (-1.74,2.93)	0.66 (-1.68,3.01)
-0.00 (-2.65,2.65)	ERTU25mg	0.47 (-1.82,2.75)	0.59 (-1.74,2.93)	0.66 (-1.68,3.01)
-0.47 (-2.75,1.82)	-0.47 (-2.75,1.82)	ERTU5mg	0.13 (-0.44,0.70)	0.20 (-0.43,0.82)
-0.59 (-2.93,1.74)	-0.59 (-2.93,1.74)	-0.13 (-0.70,0.44)	ERTU15mg	0.07 (-0.55,0.69)
-0.66 (-3.01,1.68)	-0.66 (-3.01,1.68)	-0.20 (-0.82,0.43)	-0.07 (-0.69,0.55)	Placebo

Figure.8 Results of hypoglycemia network meta analysis

3.2.2.3 Discontinuation event

The discontinuation rate of the 5mg and 15mg groups of ertugliflozin group was higher than that of the placebo group, and it was statistically significant($p<0.05$), and the difference was significant. And the discontinuation rate of 5mg group was higher than that of 15mg group, the difference was significant. There was no statistical difference between the other treatment options and the placebo control.

ERTU25mg	0.71 (-1.72,3.14)	0.81 (-1.42,3.05)	0.82 (-1.42,3.06)	0.86 (-1.36,3.08)
-0.71 (-3.14,1.72)	ERTU10mg	0.10 (-1.65,1.85)	0.11 (-1.65,1.87)	0.15 (-1.59,1.88)
-0.81 (-3.05,1.42)	-0.10 (-1.85,1.65)	Placebo	0.01 (-0.36,0.37)	0.05 (-0.30,0.40)
-0.82 (-3.06,1.42)	-0.11 (-1.87,1.65)	-0.01 (-0.37,0.36)	ERTU15mg	0.04 (-0.32,0.40)
-0.86 (-3.08,1.36)	-0.15 (-1.88,1.59)	-0.05 (-0.40,0.30)	-0.04 (-0.40,0.32)	ERTU5mg

Figure.9 Results of discontinuation event network meta analysis

3.2.3 Rank probabilistic ranking

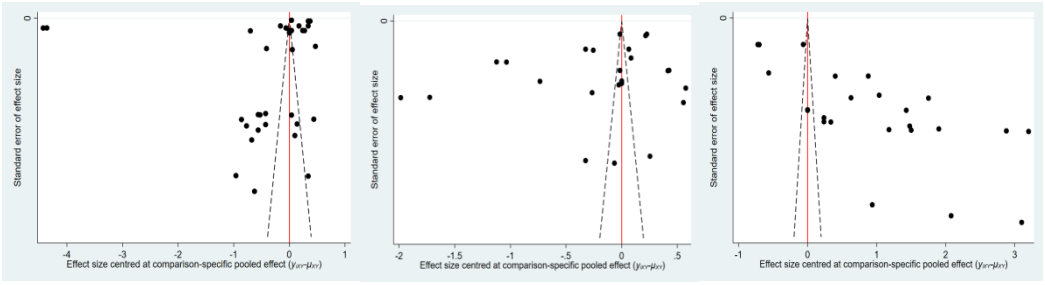
Table.2 Rank ordering values of five regimes under six end indicators

Treatment programme	HbA1C	FPG	Weight	Drug-related adverse reactions	Hypoglycemia	Discontinuation event
placebo	5	5	5	5	5	3
ERTU5mg	4	4	4	3	3	1
ERTU10mg	3	1	1	1	2	4
ERTU15mg	1	3	3	4	4	2
ERTU25mg	2	2	2	2	1	5

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

3.2.4 Publication bias analysis

Based on the analysis index of HbA1C, FPG, weight level, the combined funnel map was tested. The scattered points were asymmetric, and the scattered points basically fell outside the confidence limit and were unevenly distributed in the funnel map, which indicated that there was significant publication bias.



(A)HbA1c *(B)FDP* *(C)Body weight*

Figure.10 The funnel plot of Meta-analysis for main indexes

4. Discussion

In this study, 11 RCTs were analyzed using the network meta-analysis, involving a total of 5713 patients, and the efficacy and safety of four different doses of ertugliflozin were compared in patients with T2D. Compared to the placebo group, All treatment options can significantly reduce patient's HbA1C, only the 15mg groups was statistically significant($p<0.05$); As far as reducing FPG and body weight, All the ertugliflozin treatment groups were better than the placebo group, and all have statistical significance. According to the analysis of the grade probability diagram, 15mg and 10mg of ertugliflozin are the most effective treatment options for the treatment of T2D, which are in line with the FDA recommended dose of ertugliflozin (the starting dose is 5 mg, and the maximum daily dose is 15 mg)[20].In terms of safety, compared with the placebo group, the total adverse reaction rate, the incidence of hypoglycemia and the discontinuation of drugs due to adverse reactions, only the 15mg group and the 5mg group have significant differences in the ertugliflozin group. Among them, the 5mg group of ertugliflozin has a higher incidence of total adverse reactions and discontinuation than the 15mg treatment group, while the 15mg group has a higher incidence of hypoglycemia than the 5mg treatment group. Therefore, beware of the above risks when applying these two doses.

A total of 11 RCTs were included in this study, when the study was included,we only focused on the comparison of different doses of ertugliflozin with placebo. Due to the lack of available literature and the lack of some original data, it may have a certain impact on the evaluation. In addition, based on the included RCT results, this study only studied the efficacy and safety indicators of ertugliflozin for 52 weeks, and long-term research is needed to explore the effectiveness and safety of this product. These studies only included in English published literature, lacking of other languages or unpublished literature, and the overall quality of all the literature was average, with significant publication bias. Finally, due to differences between background treatment, sample size, treatment time and other factors, the accuracy of the study results may be affected.

In summary, ertugliflozin is a new type of SGLT2 inhibitors with remarkable effectiveness and better security,of which 15 mg and 10 mg are relatively suiTablele therapeutic doses. And ertugliflozin has entered the new version of national medical insurance catalogue of our country, has laid the foundation for further promotion and use. This study has certain clinical reference value, but due to the limited quality of the included study and the existence RCT publication bias, more high-quality RCTs studies are needed to further verified,so as to provide more evidence-based medical evidence for the treatment of ertugliflozin in T2D.

Acknowledgement

Fund programs: National Key R&D Program of China (2018YFC1311705); Construction Project of Improving Medical Service Capacity of Provincial Medical Institutions in Henan Province (2017);

ISSN 2618-1584 Vol. 3, Issue 4: 34-42, DOI: 10.25236/FMSR.2021.030407

References

[1] World Health Organization: Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed July 15, 2020.
[2] Pantalone KM, Misra-Hebert AD, Hobbs TM, et al. The probability of A1C goal attainment in patients with uncontrolled type 2 diabetes in a large integrated delivery system: a prediction model. Diabetes Care. 2020;43(8):1910–1919.https://doi.org/10.2337/dc19-0968.
[3] American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. Diabetes Care. 2020; 43(Suppl. 1):S98–S110. https://doi.org/10.2337/dc20-S009.
[4] GIACCARIA, SORICEG, MUSCOGIURIG. Glucose toxicity: the leading actor in the pathogenesis and clinical history of type 2 diabetes-mechanisms and potentials for treatment[J]. Nutr MeTable Cardiovasc Dis, 2009, 19(5) : 365-377.
[5] ROBERTSON R P,HARMON J,TRAN P O,et al. Glucose toxicity in beta-cells: type 2 diabetes,good radicals gone bad, and the glutathione connection[J]. Diabetes,2003,52 (3) : 581-587.
[6] HERMAN WH,PETERSEN M, KALYANI RR.Response to Comment on American Diabetes Asociation. Standards of Medical Care in Diabetes-2017[J]. Diabetes Care,2017,40(Suppl1):Sl-S135.
[7] HIGGINS JP, ALTMANDG, GOTZSCHE PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in ran- domised trials[J]. BMJ, 2011, 343 (182):d5928.
[8] CHENLX, LI YL, NINGGZ, et al. Comparative efficacy and tolerability of three treatments in old people with osteoporotic vertebral compression fracture: A network meta-analysis and systematic review [J]. PLOS One, 2015, 10(4):e0123153.
[9] Dagogo-Jack Samuel, Liu Jie, Eldor Roy, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: The VERTIS SITA2 placebo-controlled randomized study[J]. Diabetes Obes MeTable, 2018, 20: 530-540. PMID: 28921862.
[10] Ji Linong, Liu Yanmei, Miao Heng,et al. Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. [2019-03-04]. https://publons.com/publon/10.1111/dom.13681.
[11] Terra Steven G, Focht Kristen, Davies Melanie, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone[J]. Diabetes Obes MeTable, 2017, 19: 721-728. PMID:28116776.
[12] Amin N B, Wang X, Jain S M, et al. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin[J]. Diabetes Obes MeTable, 2015, 17: 591-598. PMID:25754396.
[13] Strojek Krzysztof, Pandey A Shekhar, Dell Vanessa, et al. Efficacy and Safety of Ertugliflozin in Patients With Diabetes Mellitus Inadequately Controlled by Sulfonylurea Monotherapy: a Substudy of VERTIS CV[J]. Diabetes Ther, 2021, 12: 1175-1192. PMID:33694093.
[14] Rosenstock Julio, Frias Juan, Pál Dénes, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET)[J]. Diabetes Obes MeTable, 2018, 20: 520-529. PMID: 28857451.
[15] Miller Sam, Krumins Tania, Zhou Haojin, et al. Ertugliflozin and Sitagliptin Co-initiation in Patients with Type 2 Diabetes: The VERTIS SITA Randomized Study[J]. Diabetes Ther, 2018, 9: 253-268. PMID:29313282.
[16] Hollander Priscilla, Liu Jie, Hill Julie, et al. Ertugliflozin Compared with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: The VERTIS SU Randomized Study[J]. Diabetes Ther, 2018, 9: 193-207. PMID:29282633.
[17] Grunberger George, Camp Sarah, Johnson Jeremy, et al. Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus: The VERTIS RENAL Randomized Study[J]. Diabetes Ther, 2018, 9: 49-66. PMID:29159457.
[18] Pratley Richard E, Eldor Roy, Raji Annaswamy, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial[J]. Diabetes Obes MeTable, 2018, 20: 1111-1120. PMID:29266675.
[19] Aronson Ronnie, Frias Juan, Goldman Allison, et al. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study[J]. Diabetes Obes MeTable, 2018, 20: 1453-1460. PMID:29419917.
[20] Ertugliflozin for Type 2 Diabetes[J]. JAMA, 2018, 319: 2434-2435. PMID:29922825.