Effectiveness and safety of sitagliptin added to metformin in real -world type 2 diabetes patients: a target trial emulation study

Xiaowei Chen

Corresponding author: Siyan Zhan, Feng Sun

Peking University

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Background

T2DM and add-on therapy

- Type 2 diabetes (T2DM) is a major public health challenge, especially in China
- Metformin is recommended as first-line therapy, but because of the progressive nature of T2DM many patients need **add-on therapy**
- **DPP-4 inhibitors (DPP-4i)** such as **sitagliptin** are popular add-on options

TTE study framework

- RCTs have demonstrated efficacy and safety of sitagliptin plus metformin
- **Limited** population-based real-world evidence (RWE) in routine clinical practice
- Unlike traditional real-world studies (RWS), employing **the target trial emulation (TTE)** study framework can reduce potential bias and enhance the credibility of causal inference

[1] Zhu D, Society C. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition)[J]. Chinese Journal of Endocrinology and Metabolism, 2021, 37: 311-398.
[2] ADA Endorses Second-Line T2D Treatments for Patients With CVD Risks[EB/OL]. https://www.uspharmacist.com/article/ada-endorses-secondline-t2d-treatments-for-patients-with-cvd-risks.
[3] Engel S S, Round E, Golm G T, et al. Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies[J]. Diabetes Ther, 2013, 4(1): 119-45.
[4] Wu D, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis[J]. Diabetes Obes Metab, 2014, 16(1): 30-7.

Objective

- To support informed clinical decisions and provide specific guidance, our study aimed to apply a **target trial emulation (TTE)** framework
- To evaluate the effectiveness and safety of adding sitagliptin to metformin, compared to metformin monotherapy, in patients with poorly controlled T2DM
- Our study could provide evidence for clinicians and guideline developers on the utility of DPP-4 inhibitor add-on therapy in usual care

Methods

Data Source

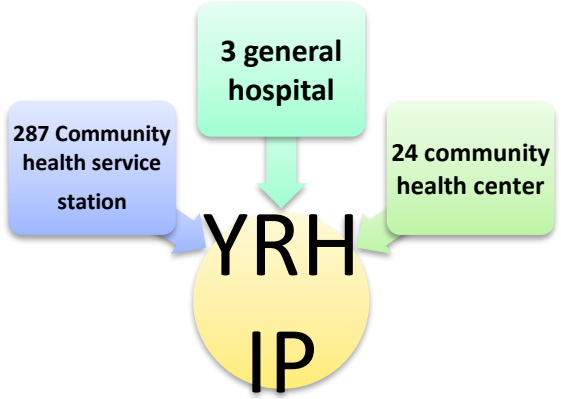
Yinzhou Regional Health Information Platform (YRHIP)

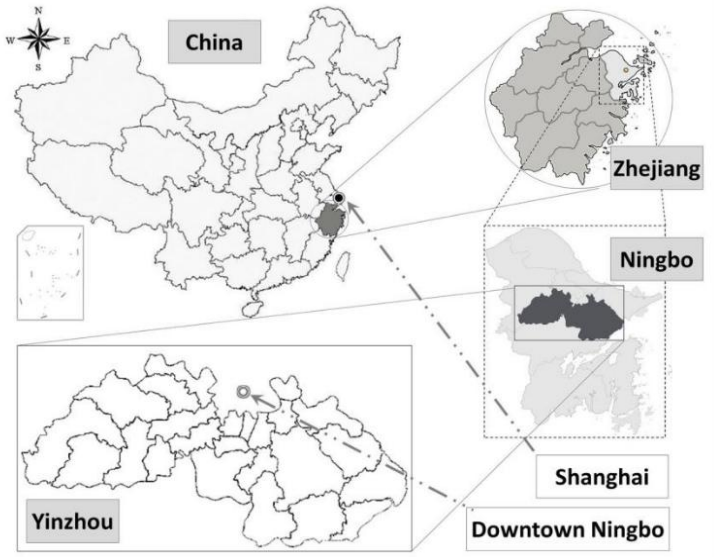
- Largest district in Ningbo
- **Stable** population： More than 98% of the permanent population, covering almost all health activities
- All Level 1 and above hospitals and their affiliated health service centers in Yinzhou District

✓ 2005 ~ 2025

✓ Cover 314 medical institutions

YRHIP Diabetes OMOP CDM





	Diabetes OMOP CDM
1	person
2	visit_occurrence
3	condition_occurrence
4	observation
5	drug_exposure
6	procedure_occurrence
7	measurement
8	death

Methods

Study design

- Target trial: Clinical.Trials.gov NCT00881530 study
- TTE study: **A sequence of nested target trials** was **emulated** including T2DM patients initiating either sitagliptin plus metformin or metformin alone from January 2017 to December 2022
- The index date for the combination therapy group was defined as the earliest sitagliptin prescription that met all eligibility criteria. For each sitagliptin initiator, we constructed a nested trial and selected one metformin-only comparator from the same 6-month calendar interval using **time-based propensity score matching (PSM)**, assigning the sitagliptin prescription date as the common index date for both patients and removing the matched comparator from subsequent time sets

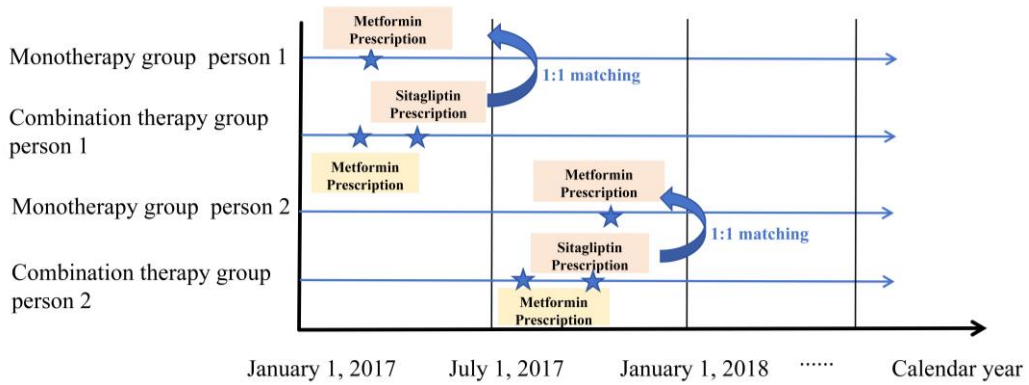


Figure. Diagram of sequential trials

Methods

Protocol component	Target trial	TTE using YRHIP Diabetes OMOP CDM
Eligibility criteria	**Inclusion criteria：** 1. Adults (≥18 and <80 years) diagnosed with T2DM, previously treated with metformin alone or with one other oral antidiabetic medication. 2. Stable metformin treatment at a daily dose ≥1500 mg. 3. Baseline HbA1c between 6.5%-9.0% (for dual therapy) or 7.0%-10.0% (for monotherapy). 4. BMI ≤40 kg/m². **Exclusion criteria**: 1. History of myocardial infarction (MI), stroke, or transient ischemic attack (TIA) within past 6 months. 2. Impaired liver or renal function. 3. CNS disorders, psychiatric illnesses, or neurological disorders potentially affecting study patients.4. Acute or chronic infections.5. Current or chronic urogenital tract infection. 6. History of clinically relevant allergy/hypersensitivity. 7. Treatment with glitazones, GLP-1RAs, insulin or weight-loss drugs within past 3 months. 8. Systemic steroid therapy or change in thyroid hormone within past 6 weeks. 9. Use of an interested drug (DPP-4 inhibitors) within past 2 months. 10.Alcohol or drug abuse. 11. Pregnancy or breastfeeding, or women of childbearing potential not using acceptable contraception.	**Inclusion criteria**: 1. Patients with a diagnosis of T2DM or unspecified diabetes, without type 1 diabetes records. 2. Prescription records of metformin prior to the index date. 3. Baseline FBG >7 mmol/L (due to limited HbA1c availability). 4. Age ≥18 and <80 years at the index date.5. BMI ≤40 kg/m² at the index date. **Exclusion criteria**: 1. History of MI, stroke, or TIA prior to the index date. 2. History of moderate/severe liver or renal disease diagnoses prior to index date. 3. Diagnosis of genitourinary tract infection within 30 days before index date. 4.Prescriptions of glitazones, GLP-1RAs, insulin, DPP-4 inhibitors, or Orlistat, systemic steroids, or thyroid hormone and analogue within 180 days before the index date. 5. Pregnancy-related diagnosis recorded within 180 days before the index date. 6. Available medical records <180 days before the index date.
Treatment strategies	Metformin at maximum tolerated dose and sitagliptin (100 mg/day) vs. metformin alone at maximum tolerated dose.	**At least one recorded prescription for sitagliptin during the follow-up period, plus a recorded metformin prescription within the 3 months preceding the sitagliptin prescription** vs **at least one recorded prescription for metformin during the follow-up period and no recorded prescriptions for DPP-4 inhibitors**.

Methods

Protocol component	Target trial	TTE using YRHIP Diabetes OMOP CDM
Treatment assignment	Randomized assignment at baseline.	Emulated randomization using propensity score matching (PSM, 1:1 nearest neighbor, caliper = 0.05) to balance baseline covariates.
Outcomes	**Efficacy outcomes**: Changes from baseline in HbA1c, FBG, body weight, waist circumference, SBP, and DBP measured at weeks 18, 30, 42, 54, 66, 78, and 90. **Safety outcomes**: Urinary tract infections, genital infections, hypoglycemic events (blood glucose ≤3.9 mmol/L, with or without hypoglycemic symptoms) within 90 weeks.	**Effective outcomes**: Same as target trial, except HbA1c omitted due to >50% missing data. **Safety outcomes**: Same as target trial.
Causal contrast	Intention-to-treat (ITT) effect.	Observational analogue of the **ITT effect**.
Follow-up	Follow-up starts the day after treatment assignment and continues until the last available outcome measurement or study end date.	Nested trials constructed every 6 months from Jan 1, 2017, to Dec 31, 2022. Follow-up begins after index date and continues until the last outcome measurement or Dec 31, 2022. Each participant is included only once to avoid variance inflation.
Statistical analysis	ITT analysis. The efficacy analyses use an analysis of covariance (ANCOVA) model with treatment group and number of previously-used antidiabetic medications as fixed effects, the corresponding baseline as a covariate, and country as a random effect.	ITT analysis. Additional PSM adjustments to emulate randomization and control baseline covariates. **Generalized estimating equations (GEE)** for effectiveness outcomes, and **logistic regression models** for safety outcomes. **Subgroup analysis**: baseline characteristics age (≤60 and >60 years), sex (female and male), smoking status, alcohol status, and duration of diabetes at the index date (≤2.5 years and >2.5 years). **Sensitivity analysis**: **per-protocol (PP) analysis.**

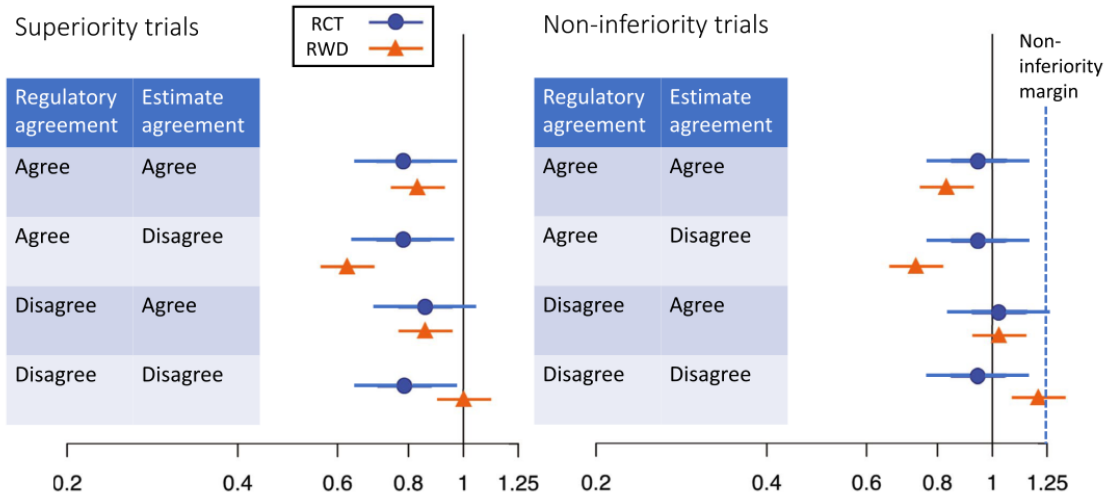
Abbreviations: PSM, propensity score matching; BMI, body mass index; CNS, central nervous system; DPP-4, dipeptidyl peptidase-4; FBG, fasting blood glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; ITT, Intention-to-treat; PP, per-protocol

Methods

Consistency Assessment

Efficacy-Effectiveness Consistency Assessment Method

To compare the TTE study results with those from RCTs, the U.S. RCT Duplicate project proposed three consistency assessment indicators:



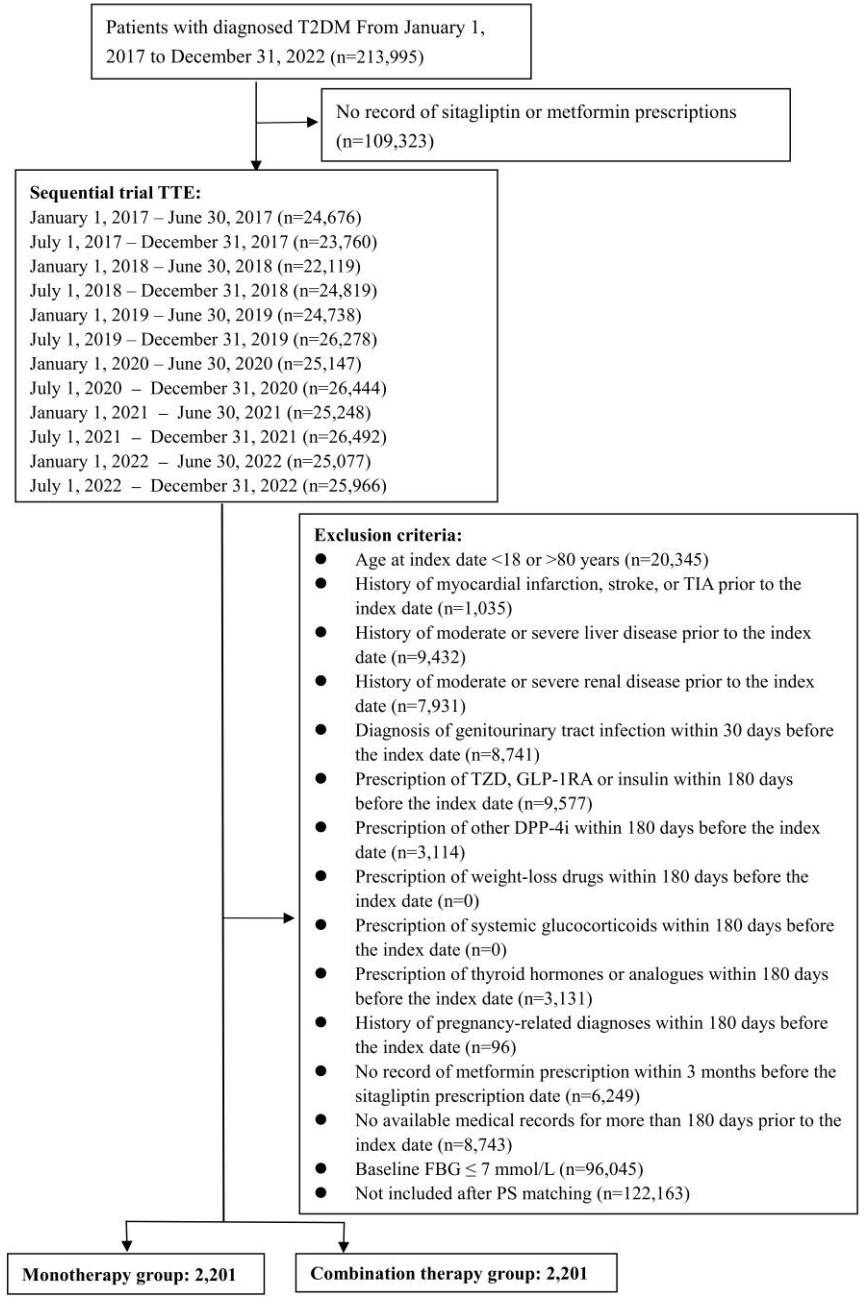
Regulatory Consistency:
whether the direction and statistical significance of treatment effects observed in RCTs are maintained in real-world studies (RWS)

Estimate Consistency:
whether the effect estimate from the real-world study (RWS) falls within the 95% confidence interval (95% CI) of the RCT results

Standardized difference:

$$Z = \frac{\theta_{RWE} - \theta_{RCT}}{\sqrt{\sigma\text{^}2_{RWE} + \sigma\text{^}2_{RCT}}}$$

Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative. Circulation. 2021;143(10):1002-1013. doi:10.1161/CIRCULATIONAHA.120.051718.



Results

- A total of 213,995 T2DM patients were identified in YRHIP in the study period, of whom 109,220 had prescription records of sitagliptin or metformin
- After applying inclusion/exclusion criteria and time-based matching, 2,201 patients each were included in the combination therapy and monotherapy groups

Figure Flowchart of participants in the TTE study

Results

Table 1. Baseline characteristics of the combination therapy and monotherapy groups after matching

Characteristic	Monotherapy group (Metformin alone)	Combination therapy group (Sitagliptin + Metformin)	SMD
Sample size	2,201	2,201	——
Sex (male)	1334 (60.6)	1326 (60.2)	0.007
Age (years)	61.72 (10.34)	61.89 (10.37)	0.017
Smoking status (yes)	518 (23.5)	515 (23.4)	0.003
Alcohol status (yes)	588 (26.7)	578 (26.3)	0.01
T2DM duration (years)	4.34 (3.77)	4.36 (3.83)	0.006
Sulfonylureas	1135 (51.6)	1156 (52.6)	0.019
Alpha-glucosidase inhibitors	644 (29.3)	635 (28.9)	0.009
SGLT-2I	116 (5.3)	133 (6.0)	0.008
Glinides	185 (8.4)	133 (6.0)	0.008
NSAIDs	604 (27.4)	636 (28.9)	0.032
Lipid-lowering agents	973 (44.2)	937 (42.6)	0.033
ACEI	657 (29.9)	634 (28.8)	0.023
ARB	77 (3.5)	82 (3.7)	0.012
Calcium channel blockers	982 (44.6)	956 (43.4)	0.024
Beta-blockers	353 (16.0)	362 (16.4)	0.011
Diuretics	415 (18.9)	435 (19.8)	0.023
PPI	375 (17.0)	380 (17.3)	0.006
Antipsychotics	53 (2.4)	56 (2.5)	0.009
Sedatives and hypnotics	284 (12.9)	290 (13.2)	0.008
Antidepressants	6 (0.3)	12 (0.5)	0.043
Antineoplastic and immunomodulating agents	8 (0.4)	8 (0.4)	<0.001
BMI (kg/m²)	24.94 ± 3.59	24.93 ± 3.38	0.003
HbA1c (%)	8.21 ± 1.99	8.26 ± 1.88	0.027
FBG (mmol/L)	9.27 ± 2.73	9.38 ± 2.46	0.043
Weight (kg)	67.59 ± 11.42	67.53 ± 10.57	0.005
Waist circumference (cm)	86.72 ± 8.92	86.67 ± 8.37	0.006
SBP (mmHg)	131.35 ±12.42	131.26 ± 13.19	0.007
DBP (mmHg)	78.59 ± 7.92	78.64 ± 8.07	0.007

- After matching, baseline characteristics were adequately balanced between the groups (all SMD <0.1)

* For continuous variables, the values are mean (SD); for categorical variables the values are number (%). T2DM, type 2 diabetes mellitus; SGLT-2I, sodium-glucose co-transporter 2 inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, Proton pump inhibitor; BMI, body mass index; FBG, fasting blood-glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Results

Effectiveness outcomes——FBG change from baseline

Table 2.1 Comparison of changes in FBG from baseline between combination therapy group and monotherapy group

Follow-up week	FBG change from baseline (Combination therapy group, mmol/L)	FBG change from baseline (Monotherapy group, mmol/L)	Point difference - MD (95% CI)	Point difference - Wald	Point difference - P value	Overall difference - MD (95% CI)	Overall difference - Wald	Overall difference - P value
18	-2.02±2.62*	-1.83±2.73*	-0.19 (-0.37, -0.01)	4.20	0.04			
30	-2.40±2.93*	-2.26±3.09*	-0.13 (-0.35, 0.09)	1.47	0.23			
42	-2.08±2.51*	-1.80±2.46*	-0.28 (-0.46, -0.10)	8.78	<0.01			
54	-2.11±2.46*	-1.82±2.56*	-0.28 (-0.46, -0.10)	8.57	<0.01	-0.22 (-0.38, -0.06)	7.26	<0.01
66	-2.07±2.39*	-1.85±2.55*	-0.22 (-0.42, -0.02)	5.23	0.02			
78	-2.03±2.32*	-1.79±2.62*	-0.25 (-0.45, -0.05)	5.99	0.01			
90	-2.03±2.36*	-1.82±2.51*	-0.22 (-0.42, -0.02)	4.38	0.04			

*: Compared with 0, the difference was statistically significant based on one-sample t-test (P < 0.05).

At all measured time points within 90 weeks except at week 30, FBG levels significantly showed greater reductions from baseline in the combination therapy group compared to the monotherapy group

Results

Effectiveness outcomes——Body weight change from baseline

Table 2.2 Comparison of changes in body weight from baseline between combination therapy group and monotherapy group

Follow-up week	Weight change from baseline (Combination therapy group, kg)	Weight change from baseline (Monotherapy group, kg)	Point difference - MD (95% CI)	Point difference - Wald	Point difference - P value	Overall difference - MD (95% CI)	Overall difference - Wald	Overall difference - P value
18	-0.11±3.85	-0.28±3.34*	0.17 (-0.08,0.42)	1.77	0.18			
30	-0.21±3.91*	-0.29±3.47*	0.08 (-0.19,0.35)	0.35	0.56			
42	-0.21±4.38*	-0.40±3.76*	0.19 (-0.10,0.48)	1.53	0.22			
54	-0.30±4.65*	-0.49±3.94*	0.19 (-0.14,0.52)	1.28	0.26	0.21 (-0.06,0.48)	2.23	0.14
66	-0.44±4.96*	-0.69±4.2*	0.24 (-0.11,0.59)	1.78	0.18			
78	-0.31±5.21*	-0.65±4.31*	0.34 (-0.05,0.73)	3.00	0.08			
90	-0.47±5.32*	-0.75±4.53*	0.28 (-0.13,0.69)	1.79	0.18			

*: Compared with 0, the difference was statistically significant based on one-sample t-test ($P < 0.05$).

Body weight decreased from baseline in the combination group at 30, 42, 66, 78, and 90 weeks. However, the differences between the two groups were not statistically significant at any measured point

Results

Effectiveness outcomes——Waist circumference change from baseline

Table 2.3 Comparison of changes in waist circumference from baseline between combination therapy group and monotherapy group

Follow-up week	Waist circumference from baseline (Combination therapy group, cm)	Waist circumference from baseline (Monotherapy group, cm)	Point difference - MD (95% CI)	Point difference - Wald	Point difference - P value	Overall difference - MD (95% CI)	Overall difference - Wald	Overall difference - P value
18	-0.04±3.88	0.03±4.03	-0.06 (-0.33,0.21)	0.67	0.74			
30	0.00±4.01	-0.03±4.15	0.04 (-0.25,0.33)	0.81	0.81			
42	0.08±4.29	0.02±4.51	0.06 (-0.25,0.37)	0.71	0.97			
54	-0.08±4.49	0.04±4.70	-0.10 (-0.45,0.25)	0.57	0.65	-0.04 (-0.33,0.25)	0.06	0.80
66	0.05±4.83	0.01±4.70	0.03 (-0.34,0.40)	0.86	0.93			
78	0.08±5.27	0.15±5.03*	-0.07 (-0.48,0.34)	0.75	0.45			
90	0.04±5.38	0.24±5.46*	-0.20 (-0.65,0.25)	0.39	0.26			

*: Compared with 0, the difference was statistically significant based on one-sample t-test (P < 0.05).

At all measured time points, the differences between the two groups in waist circumference changes from baseline were not statistically significant. During the 90-week treatment period, the overall effect of sitagliptin add-on therapy was not statistically significant

Results

Effectiveness outcomes—— SBP change from baseline

Table 2.4 Comparison of changes in SBP from baseline between combination therapy group and monotherapy group

Follow-up week	SBP change from baseline (Combination therapy group, mmHg)	SBP change from baseline (Monotherapy group, mmHg)	Point difference - MD (95% CI)	Point difference - Wald	Point difference - P value	Overall difference - MD (95% CI)	Overall difference - Wald	Overall difference - P value
18	-1.86±14.84*	-1.28±14.01*	-0.58 (-1.58,0.42)	1.28	0.26			
30	-1.78±14.11*	-0.97±14.25*	-0.81 (-1.83,0.21)	2.41	0.12			
42	-2.15±14.29*	-1.16±13.83*	-0.99 (-2.03,0.05)	3.56	0.06			
54	-1.32±14.18*	-1.21±13.82*	-0.11 (-1.17,0.95)	0.04	0.84	-0.56 (-1.4,0.28)	0.43	0.20
66	-1.53±14.38*	-0.55±13.63*	-0.98 (-2.08,0.12)	3.11	0.08			
78	-1.29±14.72*	-1.22±14.09*	-0.07 (-1.23,1.09)	0.01	0.90			
90	-1.19±14.94*	-0.95±13.63*	-0.24 (-1.44,0.96)	0.16	0.69			

*: Compared with 0, the difference was statistically significant based on one-sample t-test (P < 0.05).

SBP levels decreased from baseline at all measured points in the combination group. However, the differences between groups were not statistically significant at any point. The overall effect of combined sitagliptin on SBP over 90 weeks was not significant

Results

Effectiveness outcomes—— DBP change from baseline

Table 2.5 Comparison of changes in DBP from baseline between combination therapy group and monotherapy group

Follow-up week	DBP change from baseline (Combination therapy group, mmHg)	DBP change from baseline (Monotherapy group, mmHg)	Point difference - MD (95% CI)	Point difference - Wald	Point difference - P value	Overall difference - MD (95% CI)	Overall difference - Wald	Overall difference - P value
18	-1.36±9.37*	-0.98±8.73*	-0.38 (-1.01,0.25)	1.38	0.24			
30	-1.43±9.23*	-0.99±9.1*	-0.45 (-1.12,0.22)	1.76	0.18			
42	-1.81±9.29*	-1.19±8.97*	-0.62 (-1.29,0.05)	3.28	0.07			
54	-1.52±8.94*	-1.35±8.76*	-0.18 (-0.85,0.49)	0.27	0.61	-0.44 (-0.97,0.09)	2.7	0.10
66	-1.82±9.26*	-1.31±9.04*	-0.50 (-1.21,0.21)	1.93	0.17			
78	-1.83±8.99*	-1.62±8.56*	-0.22 (-0.93,0.49)	0.36	0.55			
90	-2.22±9.36*	-1.42±8.96*	-0.81 (-1.57,-0.05)	4.29	0.04			

*: Compared with 0, the difference was statistically significant based on one-sample t-test (P < 0.05).

DBP significantly decreased from baseline at all time points in the combination group. At week 90 , the reduction in DBP was significantly greater in the combination group vs monotherapy. However, the overall effect of combined sitagliptin on DBP over 90 weeks was not significant

Results

Safety outcomes

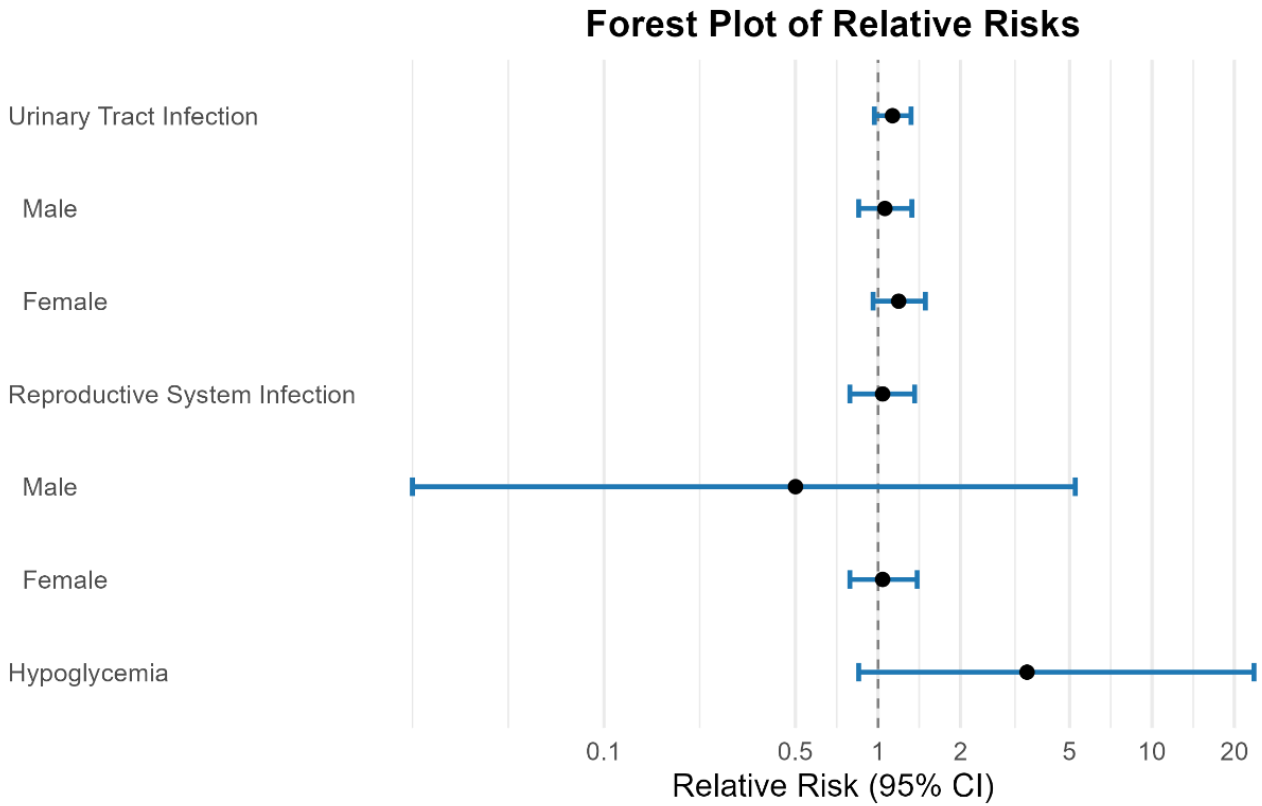


Figure Comparison of common safety outcomes between the combination therapy group and the monotherapy group

- Over 90 weeks, rates of **urinary tract infections**, **genital infections** and **hypoglycaemic events** were similar between the combination and monotherapy groups, with no statistically significant differences overall or within sex subgroups

Results

Agreement Metrics Between RCT and TTE Study Findings

Table 3 Agreement metrics between target trial and TTE study results

Outcome	RA	EA	SD
Change in FBG from baseline at week 90	×	×	×
Change in body weight from baseline at week 90	×	×	√
Change in waist circumference from baseline at week 90	√	√	√
Change in SBP from baseline at week 90	√	√	√
Change in DBP from baseline at week 90	×	×	√
Urinary tract infection	√	√	√
Male	√	√	√
Female	√	√	√
Genital infection	√	√	√
Male	√	√	√
Female	√	√	√
Hypoglycemia	√	√	√

Abbreviations: RA, Regulatory Agreement; EA, Estimate Agreement; SD, Standardized Difference.

At week 90, none of the three agreement metrics (RA, EA, SD) were met for the change in FBG from baseline. For the change in body weight from baseline at week 90, only the SD agreement was met. Changes in SBP from baseline at week 90 achieved all three agreement metrics. For DBP at week 90, only the SD agreement was met. Outcomes of urinary tract infections, genital infections, or hypoglycemic events met all agreement metrics

Results

Subgroup analysis & sensitivity analysis (brief)

- Subgroup and sensitivity analyses (PP analysis) yielded results consistent with the primary analysis

Conclusion

- This study demonstrated that initiating sitagliptin add on metformin significantly improves glycemic control in patients with poorly controlled T2DM compared to continuing metformin alone
- Dual therapy led to greater reductions in FBG, without increasing the risk of weight gain, blood pressure, hypoglycemia events, urinary tract infections or genital tract infections
- These findings corroborate evidence from RCTs by confirming that the glycemic benefits of DPP-4 inhibitor add-on therapy are achievable in the study populations. The combination of sitagliptin and metformin was well tolerated, underscoring its suitability as an early intensification strategy when monotherapy is inadequate

Thank you

Xiaowei Chen
Peking University
chen_xiaowei@hsc.pku.edu.cn