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

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Background

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. While randomized controlled trials (RCTs) have demonstrated efficacy and safety of sitagliptin plus metformin. There is lack of 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

Aims

This study aimed to conduct a target trial emulation study to evaluate the real-world effectiveness and safety of adding sitagliptin to metformin therapy versus metformin monotherapy in patients with poorly controlled T2DM.

Methods

A sequence of nested target trials (target trial: Clinical.Trials.gov NCT00881530 study) was emulated using the Yinzhou Regional Health Information Platform (YRHIP) in Ningbo, China. Patients with T2DM initiating sitagliptin combined with metformin (combination therapy group) between January 1, 2017, and December 31, 2022, were compared to those initiating metformin alone (monotherapy group), by time-based matching method. The control patients were matched via propensity scores at 6-month intervals. The primary analyses was intention-to-treat (ITT) analysis. Generalized estimating equations (GEE) were employed to evaluate changes[*] from baseline in fasting blood glucose (FBG), body weight, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at 18, 30, 42, 54, 66, 78, and 90 weeks. Logistic regression models were used to calculate the RR values and 95% confidence intervals (CI) for the corresponding safety outcomes between the groups. Findings of this TTE study were compared with RCT using predefined metrics, including statistical significance agreement (SA), estimate agreement (EA), and standardized difference (SD). Subgroup analysis was performed by 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 included per-protocol (PP) analysis.

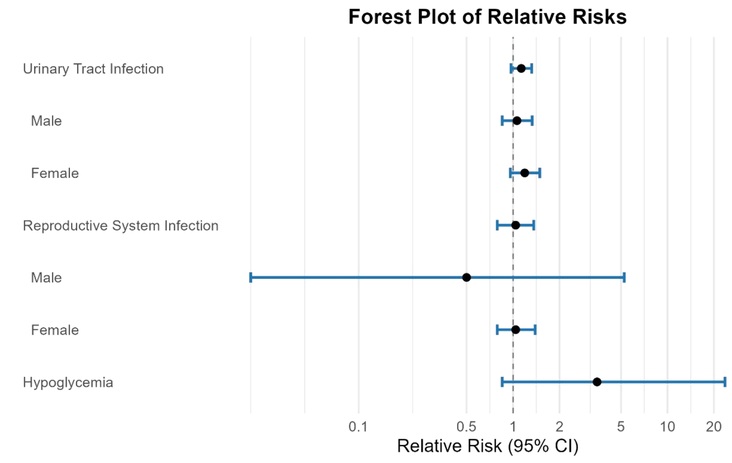

Figure Comparison of common safety outcomes between the combination therapy group and the monotherapy group

Table 2 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.

Results

A matched population of 2,201 patients were included in each group, and the baseline characteristics between the groups were effectively balanced. Combination therapy significantly reduced FBG levels compared to monotherapy group throughout the 90-week period (overall MD = -0.22, 95% CI: -0.38 to -0.06), with significant between-group differences at multiple measured points. No significant between-group differences were observed for body weight, waist circumference and SBP. DBP significantly decreased at 90 weeks (MD = -0.81, 95% CI: -1.57 to -0.05) in the combination therapy group, but the overall effect was not significant. No significant differences in safety outcomes, including urinary tract infections, genital infections, or hypoglycemic events were observed between groups. At week 90, agreement metrics between this TTE study and RCT varied by outcome. Waist circumference, SBP and safety outcomes met all agreement metrics. DBP and body weight met only SD, and FBG did not meet any metrics. Subgroup and sensitivity analyses yielded results consistent with the primary analysis.

Conclusions

In this TTE study, sitagliptin combined with metformin can effectively reduce FBG in patients with poor glycemic control compared to those treated with metformin monotherapy, without weight gain or waist circumference increase or blood pressure rise or elevated risk of hypoglycemia and common infections. These findings can reach similar conclusions as RCT, though concordance in results varied depending on some agreement metrics. The real-world evidence could support the effectiveness and safety of sitagliptin plus metformin in routine T2DM care.

Table 1.1 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			

Table 1.2 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			

Table 1.3 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			

Table 1.4 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			

Table 1.5 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).