



Efficacy and safety of metformin and sitagliptin-based dual and triple therapy in elderly Chinese patients with type 2 diabetes: Subgroup analysis of STRATEGY study

Xiangyang Liu¹ , Li Wang¹, Ying Xing¹, Samuel S Engel², Longyi Zeng³, Bin Yao³, Wen Xu³, Guojuan Chen⁴, Ye Zhang⁴, Ruya Zhang⁴, Shu Liu⁵, Jianping Weng^{3*}, Qiuhe Ji^{1*} 

¹Department of Endocrinology, Xijing Hospital, Fourth Military Medical University, Xi'an, China, ²Merck & Co, Inc, Kenilworth, New Jersey, USA, ³Department of Endocrinology and Metabolism, the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, ⁴MSD China Holding Co, Ltd, Shanghai, China, and ⁵MSD R&D (China) Co, Ltd, Beijing, China

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*Correspondence

Jianping Weng

Tel/Fax: +86-20-8525-2158

E-mail address:

wengjp@vip.163.com

Qiuhe Ji

Tel/Fax: +86-29-8477-1368

E-mail address:

jqiuhe@fmmu.edu.cn

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ABSTRACT

Aims/Introduction: To assess the efficacy and safety of metformin/sitagliptin-based dual/triple therapy in elderly Chinese patients with type 2 diabetes mellitus.

Materials and Methods: This subgroup analysis included individuals aged ≥ 65 years from the STRATEGY study, a two-stage study in which type 2 diabetes mellitus patients with unsatisfactory glycemic control on metformin were first treated with the dual combination of metformin and sitagliptin for 16 weeks ($n = 681$), and then, if glycemic control had not been achieved, were treated with a third add-on oral antihyperglycemic drug for another 24 weeks ($n = 291$). The efficacy end-point was change in glycosylated hemoglobin (HbA1c) in each stage, and the safety end-point was adverse events with a focus on hypoglycemia.

Results: At week 16, the change in HbA1c was -0.81% from baseline, and the percentages of patients who achieved HbA1c targets of $<7\%$ and $<7.5\%$ were 44.9 and 67.2%, respectively. After 24 weeks, a further average HbA1c reduction of -0.60% was observed with specific reductions of -0.70% with glimepiride, -0.63% with gliclazide, -0.51% with repaglinide and -0.45% with acarbose. The proportions of patients who achieved HbA1c targets of $<7\%$ and $<7.5\%$ were 65.4 and 81.3%, respectively, over the entire study. The rates of drug-related adverse events and hypoglycemia were, respectively, 4.1 and 4.3% in the dual therapy stage, and 5.2% and 7.1% in the triple therapy stage, without occurrence of severe hypoglycemia.

Conclusions: In elderly Chinese type 2 diabetes mellitus patients, metformin/sitagliptin-based dual and triple oral therapy can provide clinically meaningful glycemic control and is generally well tolerated with a low incidence of hypoglycemia.

INTRODUCTION

Type 2 diabetes mellitus is one of the most common chronic metabolic disorders in the elderly population. However, less than half of patients aged ≥ 65 years achieve the glycosylated hemoglobin (HbA1c) target of $<7.0\%$, and the incidence of hypoglycemia is high (15.2%) under mono- or combined oral

hypoglycemic treatments in this special patient group¹ The International Diabetes Federation global guideline for older people with type 2 diabetes mellitus and the Chinese Diabetes Society have recommended sulfonylureas, alpha-glycosidase inhibitors and dipeptide peptidase-4 (DPP-4) inhibitors as the first-line therapy, for the consideration of efficacy, safety and economic factors^{2–4}. According to the International Diabetes Federation guideline for treatment of older patients with type 2 diabetes mellitus, metformin-based dual therapy includes

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sulfonylureas and DPP-4 inhibitors as preferred partners, followed by thiazolidinediones, alpha-glycosidase inhibitors, sodium–glucose cotransporter 2 inhibitor, glucagon-like peptide-1 and insulin⁵. However, sulfonylureas, reported to be the most widely used combination with metformin in China, might increase the risk of hypoglycemia, and should be used with caution in elderly type 2 diabetes mellitus patients due to less sensitivity⁴.

Clinical inertia, defined as “recognizing the problem but failure to act”, is considered one of the major factors contributing to unsatisfactory glycemic control in the management of type 2 diabetes mellitus^{6,7}. Newly diagnosed patients do not start treatment when needed, or once patients are being treated, they are not given sufficient dosage of oral hypoglycemic agents (OHAs) or combination drug therapy in a timely manner. One of the reasons for this phenomenon is the lack of high-quality local evidence to support Guideline recommendations for clinical decisions.

DPP-4 inhibitors are a class of oral OHAs that show particular suitability for elderly patients with type 2 diabetes mellitus in China^{8,9}. Sitagliptin is a highly selective DPP-4 inhibitor that has shown strong efficacy for type 2 diabetes mellitus treatment, either as monotherapy or in combination with OHAs^{10–12}. DPP-4 inhibitors are insufficiently used in the Chinese population¹³, as this class was only included in the National Reimbursement Drug List starting in 2018. In our previous work, we evaluated the efficacy and safety of the addition of a third OHA to the metformin/sitagliptin dual therapy¹⁴. That study provided substantial evidence supporting early initiation of triple oral therapies and avoidance of clinical inertia in patients inadequately controlled with dual therapy. However, that study was carried out in the general adult population and thus, did not specifically focus on elderly patient cohorts.

Despite the recommendations by current guidelines, evidence for dual or triple combinations with DPP-4 inhibitors among elderly patients from large-scale phase IV trials is generally lacking. In this exploratory subanalysis of the STRATEGY study, we assessed the efficacy and safety profiles of metformin/sitagliptin-based dual and triple therapy in elderly Chinese patients aged ≥ 65 years, aiming to provide evidence for more treatment options for elderly type 2 diabetes mellitus patients.

METHODS

Patients

This was a post-hoc subanalysis using data obtained from the STRATEGY study (registration number NCT01709305), which was a multicenter, randomized, active-control, open-label, non-inferiority clinical trial carried out in 237 hospital-based centers in China, including 5,535 type 2 diabetes mellitus patients and consisting of two stages¹⁴: (i) a dual therapy stage (stage 1), during which type 2 diabetes mellitus patients with inadequate glycemic control (HbA1c $\geq 7.0\%$ and $\leq 10.0\%$) on metformin were treated with a stable dose of metformin/sitagliptin dual therapy for 16 weeks; and (ii) a triple therapy stage (stage 2),

in which patients who did not achieve the target HbA1c goal on dual therapy were subsequently randomized 1:1:1 into glimepiride, gliclazide, repaglinide or acarbose arms, and remained on the assigned triple therapy for 24 weeks. A schematic of the procedures of the STRATEGY study, including the inclusion and exclusion criteria in detail, is shown in Figure S1. Patients with type 1 diabetes mellitus, concomitant conditions or diseases, or specific laboratory abnormalities were excluded from the study.

According to the World Health Organization definition of elderly, an elderly person is defined as an individual aged ≥ 65 years¹⁵. As the aging process is accelerating and average life expectancy is increasing, Chinese people aged ≥ 65 years rather than 60 years was considered as elderly in the present study. Given that Chinese people have a lower baseline body mass index (BMI), BMI ≥ 24 kg/m² as a cut-off value was used to define overweight, according to the China Guidelines for Diabetes Prevention and Treatment^{16,17}.

During the study period, to decrease the incidence of hypoglycemia, the physicians adjusted doses according to the situation of each patient following the characteristics of a pragmatic trial.

The STRATEGY study was approved by each local ethical committee, and carried out in agreement with the Declaration of Helsinki.

Efficacy assessments

The primary efficacy end-point was the change in HbA1c from baseline after 16 weeks of treatment with sitagliptin + metformin dual therapy in elderly patients. The secondary efficacy end-points were: (i) the change in HbA1c from initiation of the triple therapy (week 20) to the end of the treatment (week 44); and (ii) the proportions of patients achieving target HbA1c goals of $<7\%$ and $<7.5\%$. According to the Guidelines^{4,5,18,19}, elderly individuals who are relatively healthy with few coexisting chronic illnesses and who have intact cognitive status should have a lower glycemic target (HbA1c <7.0 – 7.5%). Because the enrolled patients, as defined by the inclusion/exclusion criteria, were relatively healthy with few coexisting chronic illnesses, the target HbA1c goals of $\leq 7.0\%$ and $<7.5\%$ were considered.

Safety assessments

The proportions of patients who experienced adverse events (AEs), drug-related AEs, serious AEs and drug-related serious AEs were assessed. Serious AEs were defined as an AE that was life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in significant disability/incapacity, based on appropriate medical judgment. Gastrointestinal events, including nausea, vomiting, diarrhea and abdominal pain, in elderly patients in stage 1 and stage 2 were recorded separately.

The proportions of patients who experienced hypoglycemic events were reported. Hypoglycemic events included episodes

determined to be hypoglycemia (symptomatic or asymptomatic) and all glucose measurements ≤ 70 mg/dL (3.9 mmol/L). Symptomatic hypoglycemia was defined as any episode considered likely to represent symptomatic hypoglycemia by the investigators, which might have, but did not require, confirmatory blood glucose results. Asymptomatic hypoglycemia was defined as an asymptomatic blood glucose value ≤ 70 mg/dL. Severe hypoglycemia was defined as episodes determined to be hypoglycemia for all glucose measurements < 50 mg/dL (< 2.8 mmol/L). Severe hypoglycemia requiring medical assistance was defined as hypoglycemia with a need for hospitalization, or a call for emergency services or physicians. Recurrent hypoglycemia was defined as two or more episodes. Changes in bodyweight from baseline to weeks 20 and 44 were also measured.

Statistical analysis

For the efficacy analysis in each stage, the full analysis set population (patients who took ≥ 1 dose of study medication and had ≥ 1 outcome measured in the corresponding stage) was used. For the safety analysis in each stage, the all patients as treated population (patients who took ≥ 1 dose of study medication in the corresponding stage) was used.

Changes in HbA1c, as well as bodyweight from the initiation of triple therapy (week 20) to the end of the study (week 44) were analyzed using a longitudinal data analysis model. The goal achievement rate was descriptively summarized with point estimates and 95% confidence intervals; the last observation carried forward method was used to attribute missing values for the end-points to assess goal achievement. Safety and tolerability were assessed by a review of all safety parameters including clinical AEs, hypoglycemic events and changes in bodyweight. The between-treatment differences in the incidence rates of hypoglycemic events were compared using the χ^2 -test.

RESULTS

Baseline characteristics

A total of 681 out of 5,535 (12.3%) patients in the STRATEGY study were aged ≥ 65 years and were included in the analysis (all patients as treated), while 680 patients were included in the full analysis set population according to the predefined criteria in the STRATEGY study. Meanwhile, 261 elderly patients with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ at week 16, and a fasting finger stick glucose ≥ 7.2 and ≤ 15.6 mmol/L at week 20 proceeded to the triple therapy stage (stage 2), and received glimepiride ($n = 73$), gliclazide ($n = 76$), repaglinide ($n = 51$) or acarbose ($n = 69$) for another 24 weeks.

The demographic and other baseline characteristics of patients at the initiation of dual therapy (week 0) and initiation of triple therapy (week 20) are shown in Table 1. The mean age of elderly patients was 68.4 years, and the mean duration of diabetes was > 7.5 years. Variables at the initiation of triple therapy were comparable across the four triple therapy arms.

Efficacy

Dual therapy (stage 1)

At the end of week 16 ($n = 680$), the mean (\pm standard error) change in HbA1c from baseline was -0.81% ($\pm 0.03\%$). Subgroup data (Figure 1) showed that a greater reduction in HbA1c from baseline was achieved in male patients (-0.92%) than in female patients (-0.69% , $P < 0.001$). Changes in HbA1c from the baseline were -1.14% , -0.84% and -0.74% in patients with a disease duration of < 1 year, 1–5 years and > 5 years ($P < 0.001$). Patients with higher baseline HbA1c values had greater reductions in HbA1c of -1.72% , -0.88% and -0.56% for patients with a baseline HbA1c of $\geq 9.0\%$, $\geq 8.0\%$ to $< 9.0\%$ and $< 8.0\%$, respectively ($P < 0.001$). A similar reduction in HbA1c was observed in patients with a BMI > 24 kg/m² and ≤ 24 kg/m² (-0.81% vs -0.79% , $P = 0.695$). The HbA1c reduction was also similar for patients with an estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m² and 60 to < 90 mL/min/1.73 m² (-0.76% vs -0.87% , $P = 0.104$).

Totals percentages of 44.9% ($n = 305$) and 67.2% ($n = 457$) of patients met the HbA1c goals of $< 7.0\%$ and $< 7.5\%$ at week 16, respectively. The proportions of patients achieving the HbA1c target goal during the dual therapy stage are shown in Figure 2a. All the effects were achieved under the average daily dosages of 1552.8 ± 198.7 mg metformin and 100.0 ± 0.0 mg sitagliptin.

Triple therapy (stage 2)

At the end of week 44, the mean (\pm standard error) change in HbA1c from baseline (week 20) was -0.60% ($\pm 0.05\%$). The mean HbA1c reductions in the glimepiride, gliclazide, repaglinide and acarbose groups were 0.70%, 0.63%, 0.51% and 0.45%, respectively (Figure 3a). Notably, triple therapy with glimepiride induced a more significant HbA1c reduction than did triple therapy with acarbose ($P = 0.047$, glimepiride vs acarbose group). On stratification of patients by BMI values, the mean changes in HbA1c from baseline (week 20) to 44 weeks were -0.57% ($\pm 0.07\%$) and -0.64% ($\pm 0.08\%$) in patients with a BMI > 24 kg/m² and ≤ 24 kg/m², respectively. Among patients with a BMI > 24 kg/m², the four triple therapy arms caused similar HbA1c responses (glimepiride, -0.66% ; gliclazide, -0.71% ; repaglinide, -0.37% ; acarbose, -0.40% ; Figure 3b). On stratification of patients by eGFR values, the mean HbA1c change was -0.65% ($\pm 0.07\%$) in patients with an eGFR ≥ 90 mL/min/1.73 m² and -0.55% ($\pm 0.07\%$) in patients with an eGFR 60 to < 90 mL/min/1.73 m², with the greatest reduction observed in the glimepiride group (-0.88%) as compared with the repaglinide (-0.40% , $P = 0.023$) and acarbose (-0.50% , $P = 0.053$) groups. No significant differences were found in HbA1c changes across the four triple therapy arms among patients with an eGFR 60 to < 90 mL/min/1.73m², with HbA1c changes ranging from -0.37% (acarbose) to -0.69% (repaglinide; Figure 3c).

The proportions of patients who achieved HbA1c levels of $< 7.0\%$ and $< 7.5\%$ were 52.8% ($n = 142$) and 72.1% ($n = 194$), respectively, during the triple therapy stage (Figure 2b). All the effects were achieved under an average daily dosage of

Table 1 | Baseline characteristics of patients who received dual and triple therapy (full analysis set population)

Characteristics	Dual therapy (n = 680)	Triple therapy				
		Total (n = 269)	Glimepiride (n = 73)	Gliclazide (n = 76)	Repaglinide (n = 51)	Acarbose (n = 69)
Age (years)	68.4 ± 2.8	68.4 ± 2.9	68.6 ± 2.7	68.2 ± 3.0	68.8 ± 3.0	68.3 ± 3.1
Male, n (%)	344 (50.5)	129 (48.0)	37 (50.7)	34 (44.7)	23 (45.1)	35 (50.7)
Duration of diabetes (years)	7.5 ± 5.4	8.3 ± 5.2	8.6 ± 5.3	8.6 ± 5.2	8.2 ± 5.3	7.6 ± 4.9
Weight (kg)	66.7 ± 11.1	66.4 ± 11.2	66.7 ± 10.4	65.4 ± 12.1	66.8 ± 10.7	67.0 ± 11.4
BMI (kg/m ²)	25.0 ± 3.2	24.9 ± 3.1	24.9 ± 3.2	24.5 ± 3.2	25.2 ± 3.2	25.0 ± 2.8
Medical history or concurrent disease, n (%)						
Hyperlipidemia	212 (31.1)	64 (23.8)	11 (15.1)	26 (34.2)	9 (17.6)	18 (26.1)
Hypertension	315 (46.3)	120 (44.6)	30 (41.1)	36 (47.4)	24 (47.1)	30 (43.5)
Hepatic steatosis	28 (4.1)	9 (3.3)	3 (4.1)	2 (2.6)	2 (3.9)	2 (2.9)
Coronary artery disease	63 (9.3)	27 (10.0)	3 (4.1)	10 (13.2)	5 (9.8)	9 (13.0)
LDL (mg/dL)	104.4 ± 30.9	108.3 ± 30.9	119.9 ± 27.1	104.4 ± 34.8	104.4 ± 30.9	104.4 ± 30.9
Total cholesterol (mg/dL)	181.7 ± 38.7	181.7 ± 38.7	185.6 ± 33.4	185.6 ± 46.4	185.6 ± 38.7	174.0 ± 34.8
Triglyceride (mg/dL)	141.7 ± 88.6	141.7 ± 97.4	132.9 ± 62.0	150.6 ± 79.7	141.7 ± 79.7	141.7 ± 159.4
HDL (mg/dL)	50.3 ± 11.6	50.3 ± 11.6	50.3 ± 11.6	46.4 ± 11.6	50.3 ± 15.5	50.3 ± 11.6
BUN (mg/dL)	15.7 ± 4.5	15.4 ± 3.9	15.1 ± 4.2	15.7 ± 3.9	15.4 ± 3.4	15.7 ± 4.2
Creatinine (mg/dL)	0.75 ± 0.18	0.74 ± 0.18	0.75 ± 0.16	0.72 ± 0.18	0.73 ± 0.20	0.75 ± 0.19
eGFR (mL/min/1.73m ²)	95.0 ± 23.6	95.9 ± 22.5	94.3 ± 21.3	98.1 ± 23.1	97.3 ± 24.4	94.4 ± 21.8
eGFR ≥90 mL/min/1.73 m ² , n (%)	385 (56.6)	145 (53.9)	34 (46.6)	46 (60.5)	28 (54.9)	37 (53.6)
eGFR 60–89 mL/min/1.73 m ² , n (%)	274 (40.3)	117 (43.5)	38 (52.1)	30 (39.5)	20 (39.2)	29 (42.0)
eGFR <60 mL/min/1.73 m ² , n (%)	21 (3.7)	7 (2.6)	1 (1.4)	0 (0)	3 (5.9)	3 (4.3)
Baseline HbA1c (%)	8.0 ± 0.8	7.64 ± 0.74	7.62 ± 0.82	7.68 ± 0.76	7.69 ± 0.70	7.59 ± 0.69
HbA1c <8.0%, n (%)	385 (56.6)	193 (71.7)	52 (71.2)	55 (72.4)	31 (60.8)	55 (79.7)
HbA1c ≥8.0% and <9.0%, n (%)	204 (30.0)	62 (23.0)	16 (21.9)	16 (21.1)	19 (37.3)	11 (15.9)
HbA1c ≥9.0%, n (%)	91 (13.4)	14 (5.2)	5 (6.8)	5 (6.6)	1 (2.0)	3 (4.3)
OADs at screening, n (%)						
Biguanides [†]	221 (32.5)	93 (34.6)	23 (31.5)	28 (36.8)	18 (35.3)	24 (34.8)
SUs [‡]	67 (9.9)	33 (12.3)	6 (8.2)	9 (11.8)	7 (13.7)	11 (15.9)
Alpha-glucosidase inhibitor	16 (2.4)	8 (3.0)	2 (2.7)	2 (2.6)	1 (2.0)	3 (4.3)
Other OHAs	20 (2.9)	7 (2.6)	1 (1.4)	5 (6.6)	0	1 (1.4)
HbA1c at 44 weeks (%)	–	7.04 ± 0.82	6.90 ± 0.84	7.03 ± 0.72	7.15 ± 1.07	7.13 ± 0.68

Data are presented as mean ± standard deviation or n (%). [†]Including metformin and metformin hydrochloride. [‡]Including sulfonamides and sulfonyleurea derivatives. BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein cholesterol; OHAs, oral antihyperglycemic agents; SUs, sulfonylureas.

1561.9 ± 236.9 mg metformin and 100.0 ± 0.0 mg sitagliptin, with a third OHA (1.7 ± 0.7 mg glimepiride, 38.3 ± 15.2 mg gli-clazide, 1.9 ± 0.8 mg repaglinide or 153.3 ± 30.0 mg acarbose).

Overall HbA1c achievement

Through the initial treatment with metformin + sitagliptin for 20 weeks and addition of a third OHA for those who were inadequately controlled with dual therapy for another 24 weeks, the proportions of patients eventually achieving HbA1c target goals of <7% and <7.5% were 65.4% and 81.3%, respectively, during the entire study (Figure 2c).

Safety analysis

AEs

During the dual therapy period, 29.7% (n = 202) of patients had at least one AE (Table 2), and just 4.1% patients had

drug-related AEs. Serious AEs were reported in 15 (2.2%) patients, and only one patient experienced serious study drug-related AEs. One death was reported to be due to gallbladder carcinoma, but not related to the drug. Discontinuation due to AEs occurred in 11 (1.6%) patients.

During the triple therapy stage, AEs and drug-related AEs were reported in 83 (30.9%) and 14 (5.2%) patients, respectively. Serious AEs occurred in nine (3.3%) patients, and none of the serious AEs were considered drug-related. The proportions of patients who experienced AEs were similar across the four triple therapy groups (glimepiride, 34.2%; gli-clazide, 30.3%; repaglinide, 33.3%; and acarbose, 26.1%), but the repaglinide group had a relatively higher frequency of drug-related AEs (11.8%) compared with the other groups (glimepiride, 6.8%; gli-clazide, 2.6%; and acarbose, 1.4%). There were no deaths reported during the triple therapy stage.

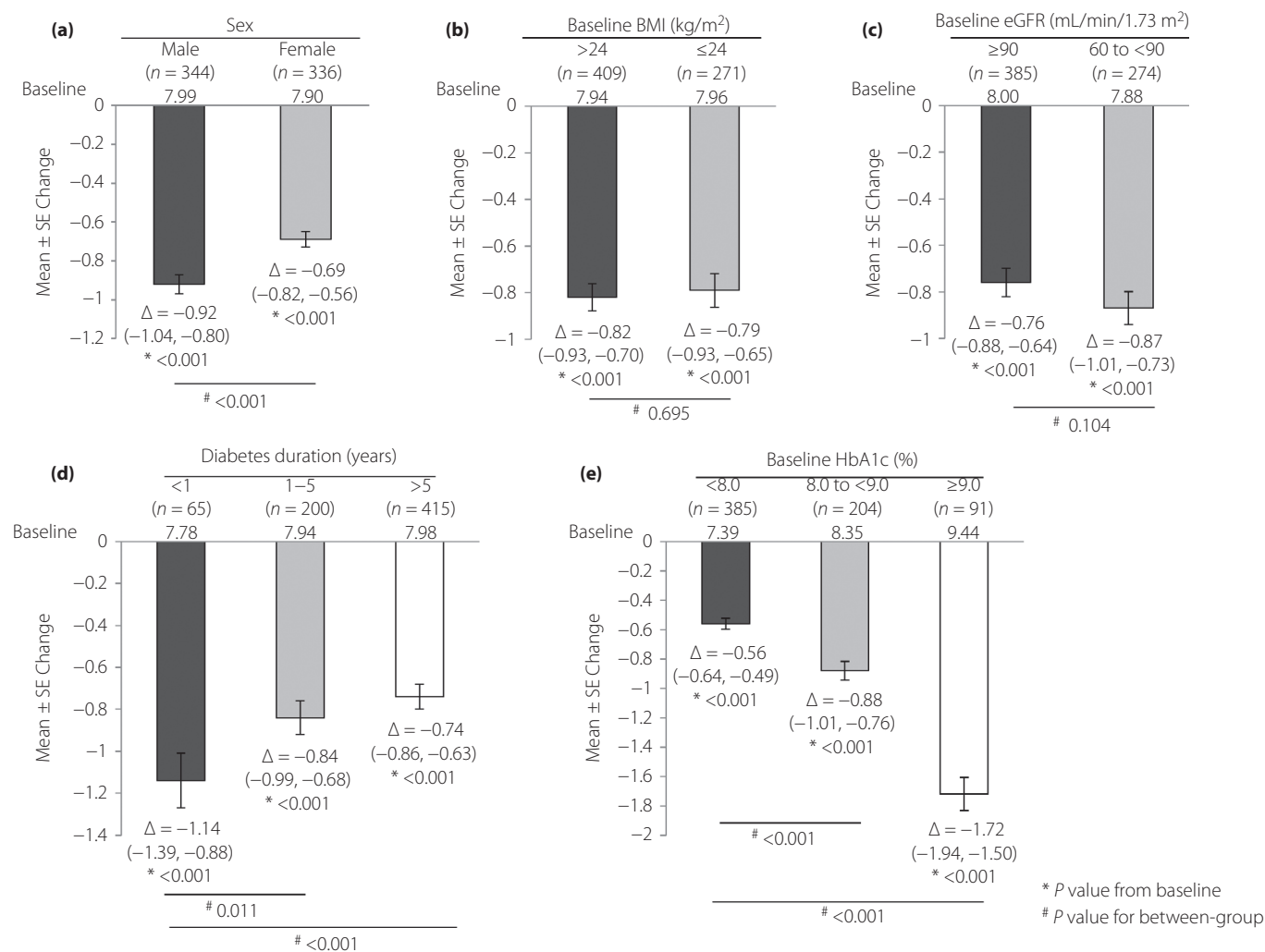


Figure 1 | Change in glycated hemoglobin (HbA1c; %) from baseline to the end of week 16 in patient subgroups. The data were analyzed through stratification of patients by (a) sex, (b) baseline body mass index (BMI), (c) baseline estimated glomerular filtration rate (eGFR), (d) diabetes duration and (e) baseline HbA1c.

Hypoglycemia

The incidence of hypoglycemia was 4.3% in the dual therapy stage, with 0.9% being asymptomatic hypoglycemia and 1.9% being recurrent hypoglycemia. In the triple therapy stage, the incidence of hypoglycemia, as compared with that in the glimepiride group (9.6%), was reported to be similar in the gliclazide and repaglinide groups (10.5 and 5.9%, respectively), but patients in the acarbose group had significantly fewer hypoglycemic events (1.4%, $P = 0.036$; Table 2). No severe hypoglycemic events occurred throughout the entire study period.

Bodyweight

At the end of week 20, the mean change in bodyweight from baseline was $-0.31 \text{ kg} \pm 0.09$ after the dual therapy stage. The addition of a third OHA to metformin + sitagliptin induced slight weight changes from baseline (week 20), such as $-$

$0.23 \text{ kg} (\pm 0.26 \text{ kg})$ in the glimepiride group, $0.03 \text{ kg} (\pm 0.35 \text{ kg})$ in the gliclazide group, $-0.15 \text{ kg} (\pm 0.45 \text{ kg})$ in the repaglinide group and $-1.44 \text{ kg} (\pm 0.26 \text{ kg})$ in the acarbose group (Figure 3d). Triple therapy with acarbose caused more significant weight change than triple therapy with glimepiride ($P = 0.001$).

DISCUSSION

This was a post-hoc subanalysis of the STRATEGY study. Despite mean baseline HbA1c values of 8.0%, with a relatively long diabetes duration and >43% of patients having mild renal impairment (chronic kidney disease stage 2), >81% of elderly patients with type 2 diabetes mellitus achieved the target HbA1c of <7.5% after 44 weeks of treatment with metformin + sitagliptin-based dual/triple therapy, with a low incidence of hypoglycemia and no change or only a slight reduction in bodyweight.

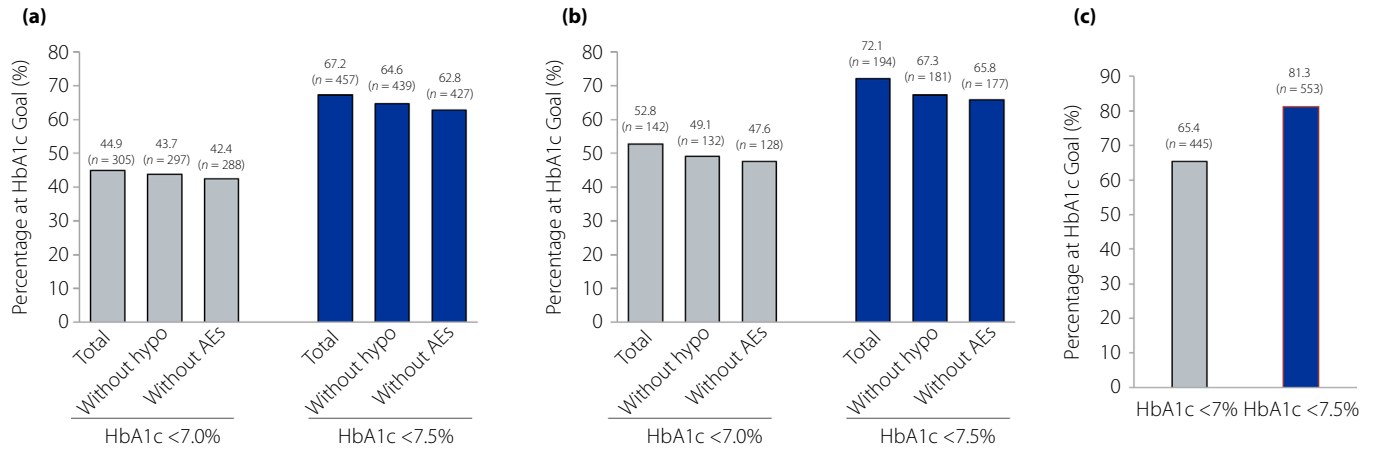


Figure 2 | Percentage of patients who achieved glycemic goals of glycated hemoglobin (HbA1c) <7% and <7.5% (full analysis set population). (a) During the dual stage (at week 16); (b) during the triple stage (at week 44); and (c) during the entire study period. AEs, adverse events; hypo, hypoglycemia.

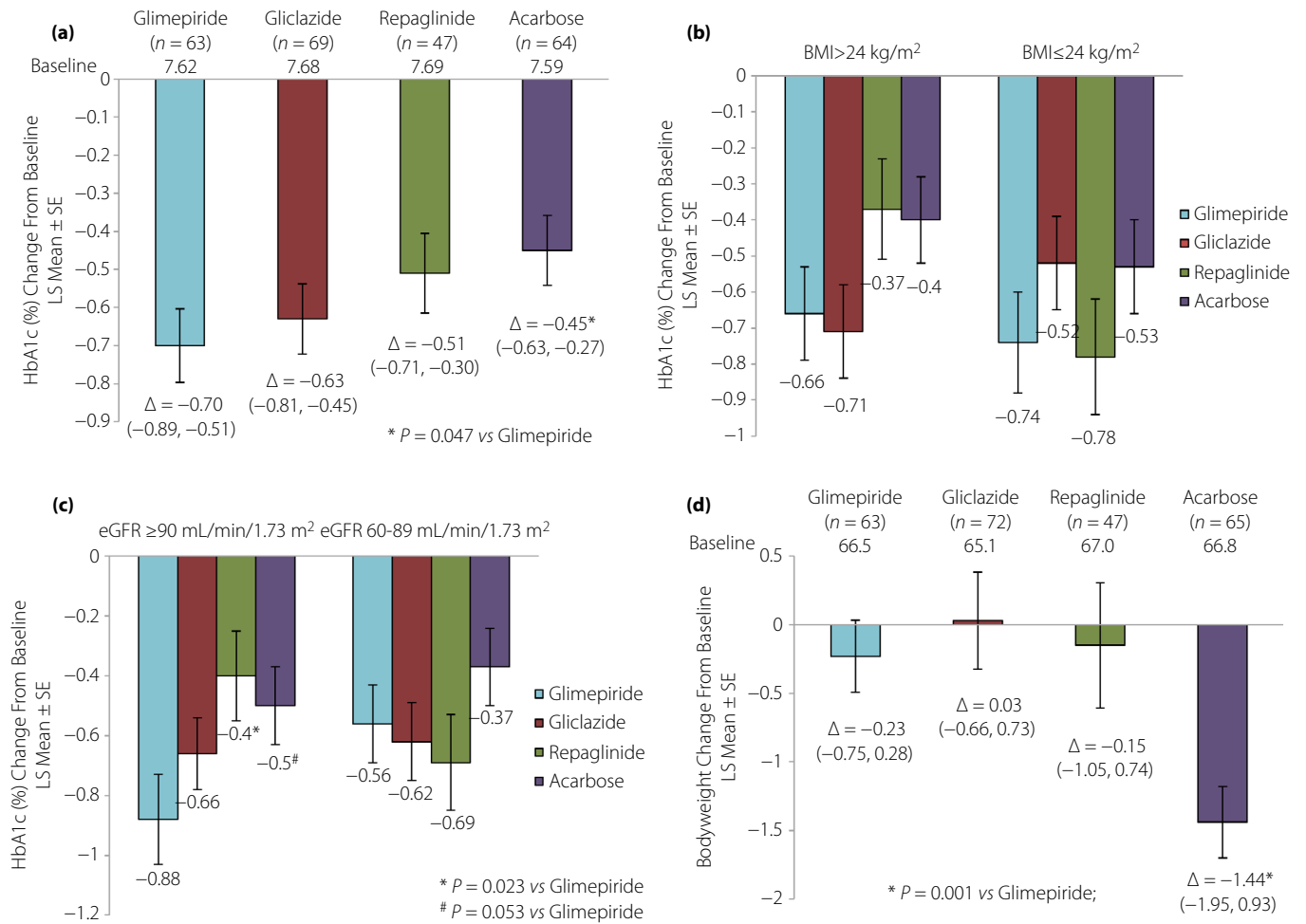


Figure 3 | Changes in glycated hemoglobin (HbA1c; %) and bodyweight from baseline to the end of week 44 in the overall cohort and subgroups of patients. (a) Change in HbA1c (%) from baseline (week 20) to week 44; (b) change in HbA1c (%) from baseline (week 20) to week 44 in patient subgroups by body mass index (BMI) stratification; (c) change in HbA1c (%) from baseline (week 20) to week 44 in patient subgroups by estimated glomerular filtration rate stratification; (d) change in bodyweight (kg) from baseline (week 20) to week 44. SE, standard error.

Table 2 | Incidence of adverse events and hypoglycemia in the dual and triple therapy stages (all patients as treated population)

	Dual therapy (<i>n</i> = 681)	Triple therapy				
		Total (<i>n</i> = 269)	Glimepiride (<i>n</i> = 73)	Gliclazide (<i>n</i> = 76)	Repaglinide (<i>n</i> = 51)	Acarbose (<i>n</i> = 69)
AEs						
Any AEs	202 (29.7)	83 (30.9)	25 (34.2)	23 (30.3)	17 (33.3)	18 (26.1)
Drug-related [†] AEs	28 (4.1)	14 (5.2)	5 (6.8)	2 (2.6)	6 (11.8)	1 (1.4)
Any SAEs	15 (2.2)	9 (3.3)	1 (1.4)	3 (3.9)	2 (3.9)	3 (4.3)
Drug-related SAEs	1 (0.1)	0	0	0	0	0
AEs leading to discontinuation	11 (1.6)	6 (2.2)	2 (2.7)	1 (1.3)	2 (3.9)	1 (1.4)
Death	1 (0.1) [‡]	0	0	0	0	0
Nausea	0	0	0	0	0	0
Vomiting	0	1 (0.4)	1 (1.4)	0	0	0
Diarrhea	3 (0.4)	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0
Hypoglycemia						
Any hypo	29 (4.3)	19 (7.1)	7 (9.6)	8 (10.5)*	3 (5.9)**	1 (1.4)***
Asymptomatic hypo	6 (0.9)	3 (1.1)	1 (1.4)	1 (1.3)	1 (2.0)	0
Symptomatic hypo	27 (4.0)	18 (6.7)	6 (8.2)	8 (10.5)	3 (5.9)	1 (1.4)
Severe hypo	0	0	0	0	0	0
Severe hypo requiring medical assistance [†]	0	0	0	0	0	0
Recurrent hypo [‡]	13 (1.9)	8 (3.0)	3 (4.1)	4 (5.3)	1 (2.0)	0

[†]Data presented as, *n* (%). Assessed by the investigator as related to the study drug. [‡]Caused by gallbladder adenocarcinoma, not drug-related. **P* = 0.849, ***P* = 0.456, ****P* = 0.036 compared with glimepiride. AEs, adverse events; hypo, hypoglycemia; SAEs, serious adverse events.

In the present study, elderly patients with type 2 diabetes mellitus showed similar reductions in HbA1c (−0.81%), as well as overall incidences of AEs (29.7%) in the dual therapy stage compared with general patients of all ages in the STRATEGY study (−0.85% and 29.2%, respectively). This result has also been confirmed by the results of a meta-analysis, which showed that the use of DPP-4 inhibitors as monotherapy or in combination with other OHAs including metformin led to a mean HbA1c reduction of −0.7% to −1.2% in patients aged ≥65 years, and this HbA1c-lowering effect was similar to that in younger patients²⁰.

Data have suggested that approximately 50% of Chinese people aged ≥65 years are either overweight or obese²¹. We found no significant difference in HbA1c reduction between patients with BMI >24 kg/m² and ≤24 kg/m². This suggests that the baseline BMI was not associated with the efficacy of metformin + sitagliptin-based therapy on HbA1c reduction. Renal impairment occurs in 20–43% of patients with a history of diabetes, and might develop independently or secondary to diabetes^{22,23}. This incidence might be even higher in elderly patients with type 2 diabetes mellitus, given that this population has a longer duration of diabetes and age-related declination in eGFR, as compared with younger patients²⁴. The presence of renal impairment might increase the risk of hypoglycemia and make treatment strategies more complicated²⁵. The present findings suggest that the HbA1c reduction was similar for patients with an eGFR ≥90 mL/min/1.73 m² and 60 to <90 mL/min/1.73 m² in both dual and triple therapy stages,

suggesting that the efficacy of metformin/sitagliptin-based therapy was independent of renal function in elderly type 2 diabetes mellitus patients. As expected, the use of sitagliptin resulted in a greater HbA1c reduction in patients whose baseline HbA1c levels were higher. Although elderly patients with higher baseline HbA1c levels might apparently be more responsive to pharmacological treatment, they are, on the contrary, unlikely to achieve the target HbA1c goal¹⁴. In addition, elderly patients with short disease duration were more likely to achieve greater glycemic improvement, suggesting the benefits of earlier initiation of the combination therapy. In the present study, a greater reduction in HbA1c from baseline was observed in male patients than in female patients with the dual therapy with metformin/sitagliptin. It is unclear whether the difference could simply be due to chance, as prior studies with sitagliptin have not shown any sex effect.

The treatment goal for elderly type 2 diabetes mellitus patients is to ideally balance the benefits of effective glycemic control and the risk of drug-associated AEs, particularly hypoglycemia^{5,18,26}. As recommended by guidelines, when inadequate control is experienced with dual therapy, insulin therapy can be initiated. However, insulin therapy has a high risk of hypoglycemia, and there are several contraindications for insulin use in elderly patients, including age-related changes in functional abilities and senses²⁷. The International Diabetes Federation Clinical Practice Recommendations for managing type 2 diabetes mellitus proposed that triple therapy with three oral OHAs might be an alternative before starting injectable

insulin²⁸, suggesting the importance of treatment strategies using multiple classes of glucose-lowering medications. In the present study, the potent glucose-lowering actions of sulfonylureas as a third add-on agent to metformin/sitagliptin-based dual therapy were observed. However, sulfonylurea treatment is associated with a potential risk of hypoglycemia, which is especially problematic for elderly patients^{18,19,29}. Despite the associated risk of hypoglycemia, sulfonylureas, usually in conjunction with glucosidase inhibitors or metformin, are commonly used for elderly patients with type 2 diabetes mellitus in China¹. Acarbose, an alfa-glucosidase, exerts its glucose-lowering effect by impeding the rate of carbohydrate digestion. Triple combination with acarbose hardly causes hypoglycemia, but promotes weight loss in the elderly. However, acarbose was associated with frequent gastrointestinal side-effects.

DPP-4 inhibitors have been reported not to increase the risk of hypoglycemia among elderly patients with type 2 diabetes mellitus³⁰. Previous studies showed a similar glucose-lowering effect, but significantly lower risk of overtreatment (HbA1c <6.5%) or hypoglycemia when adopting an add-on therapy with sitagliptin compared with sulphonylureas in older adults^{31,32}. In the 2015 American Diabetes Association/European Association for the Study of Diabetes position statement update, DPP-4 inhibitors are recommended as alternatives to metformin monotherapy if there is an intolerance, or as add-on second-line agents if blood glucose is suboptimal³³. This emphasized the benefits of DPP-4 inhibitors in the treatment of type 2 diabetes mellitus. However, currently there is little experience in the treatment of elderly diabetes patients with dual- or triple- combination agents. The present results showed that almost half of the elderly patients who were treated with metformin and sitagliptin for 16 weeks achieved the glycemic goals without significant adverse effects, which further confirmed the recommendations of the guideline. For those patients who did not achieve glycemic target, metformin and sitagliptin-based triple therapy was found to be safe and effective.

The present study had notable strengths. When designing the study, the investigators fully considered the “treatment inertia” of Chinese patients with type 2 diabetes mellitus, and selected the representative antihyperglycemic agents in China. Also, this was the first national multicenter, comparative study with a large sample size to evaluate the efficacy and safety of the metformin/sitagliptin-based dual and triple therapy in elderly Chinese patients with type 2 diabetes mellitus. Such large-scale clinical studies are rare both globally and in China. In particular, the results of the study, in agreement with guideline recommendations, provide solid evidence for making patient-centered treatment decisions for those elderly patients who are unable to achieve or maintain glycemic targets without increasing hypoglycemia.

The present study also had some limitations. The STRATEGY study did not include some categories of OHAs, such as sodium–glucose cotransporter 2 inhibitors, which were not available at that time in China, and thiazolidinediones, which are infrequently used in China. Second, we did not analyze possible alterations in the elderly patients in other aspects; for

instance, lipid profiles, cardiovascular risk and so on. Other limitations included the relatively small sample size for subgroup analysis, the short treatment period and the restriction to patients from China.

In conclusion, the present findings provide evidence that metformin/sitagliptin-based dual therapy can significantly improve glycemic control in elderly Chinese type 2 diabetes mellitus patients with unsatisfactory glycemic control on metformin, even in those with a long duration of diabetes, mild chronic kidney disease or overweight/obesity. The addition of a third add-on agent, including glimepiride, gliclazide, repaglinide or acarbose, was relatively well-tolerated with a neutral effect on weight, and can further improve glycemic control in elderly type 2 diabetes mellitus patients. Although a DPP-4 inhibitor is recommended as a second-line antihyperglycemic agent in guidelines, there is a lack of large-scale clinical studies to validate its safety and efficacy in elderly patients. The present study provides a basis for formulating guideline recommendations, as well as developing treatment strategies for elderly Chinese patients with type 2 diabetes mellitus.

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DISCLOSURE

SE is an employee of Merck & Co., Inc., Kenilworth, NJ, USA. GC, YZ and RZ are employees of MSD China, Shanghai, China. SL is an employee of MSD R&D (China) Co., Ltd. JW received travel support from Merck & Co., Inc. for the STRATEGY study. JW has received grants from Novo Nordisk, Eli Lilly, Sanofi Aventis and Bayer for National T1DM Registration Study while the study was being carried out. JW is also a data safety monitoring board member for the ACE study. He has attended the advisory boards, and has been a speaker of Sanofi Aventis, AstraZeneca, Medtronic and Hengrui Pharmaceuticals Company. QJ received travel support as an advisory boards member from Merck & Co., Inc for the STRATEGY study; he has attended advisory boards and been a speaker of Eli Lilly, Novo Nordisk, Merck Sharp & Dohme China, Sanofi Aventis, Hua-dong Pharmaceuticals Company and Medtronic; and received research grants from Novo Nordisk, Merck Sharp & Dohme China and AstraZeneca. The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Schematic of the procedures of the STRATEGY study. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HIV, human immunodeficiency virus; TSH, thyroid stimulating hormone.