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CLINICAL TRIAL

Oral glucose lowering with linagliptin and metformin compared with linagliptin alone as initial treatment in Asian patients with newly diagnosed type 2 diabetes and marked hyperglycemia: Subgroup analysis of a randomized clinical trial

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ABSTRACT

Aims/Introduction: Type 2 diabetes mellitus is an epidemic in Asia, yet clinical trials of glucose-lowering therapies often enroll predominantly Western populations. We explored the initial combination of metformin and linagliptin, a dipeptidyl peptidase-4 inhibitor, in newly diagnosed type 2 diabetes mellitus patients in Asia with marked hyperglycemia.

Materials and Methods: This was a post-hoc subgroup analysis of a multinational, parallel-group clinical trial in which 316 newly diagnosed type 2 diabetes mellitus patients with glycated hemoglobin A1c (HbA1c) 8.5–12.0% were randomized to double-blind oral treatment with linagliptin/metformin or linagliptin monotherapy. The primary end-point was the change from baseline in HbA1c at week 24. We evaluated data for the 125 participants from Asian countries.

Results: After 24 weeks, the mean ± standard error reduction from baseline in HbA1c (mean 10.0%) was −2.99 ± 0.18% with linagliptin/metformin and −1.84 ± 0.18% with linagliptin; a treatment difference of −1.15% (95% confidence interval −1.65 to −0.66, $P < 0.0001$). HbA1c <7.0% was achieved by 60% of participants receiving linagliptin/metformin. The mean bodyweight change after 24 weeks was −0.45 ± 0.41 kg and 1.33 ± 0.45 kg in the linagliptin/metformin and linagliptin groups, respectively (treatment difference −1.78 kg [95% confidence interval −2.99 to −0.57, $P = 0.0043$]). Drug-related adverse events occurred in 9.7% of participants receiving linagliptin/metformin and 4.8% of those receiving linagliptin. Hypoglycemia occurred in 6.5% and 4.8% of the linagliptin/metformin and linagliptin groups, respectively, with no severe episodes. Gastrointestinal disorders occurred in 12.9% and 12.7% of the linagliptin/metformin and linagliptin groups, respectively, with no associated treatment discontinuations.

Conclusions: In people from Asia with newly diagnosed type 2 diabetes mellitus and marked hyperglycemia, the initial combination of linagliptin and metformin substantially improved glycemic control without weight gain and with infrequent hypoglycemia. Initial oral combination therapy might be a viable treatment for such individuals.

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INTRODUCTION

The prevalence of type 2 diabetes mellitus in Asian countries has increased substantially in recent decades, driven predominantly by rapid economic development and associated lifestyle changes fueling increases in obesity, although environmental, genetic and epigenetic factors might also play a role[1–5]. Consequently, 232 million of the estimated 415 million people globally with diabetes live in the Western Pacific and Southeast Asian regions, with China and India together accounting for approximately one-half of these individuals[6].

Compared with their Caucasian counterparts, Asians with type 2 diabetes mellitus have several clinically important differences at a population level, including younger age, lower body-mass index (BMI) and reduced β-cell function (especially in East Asians), with many patients requiring early insulin treatment[3,4]. Also notable are greater abdominal obesity with more insulin resistance (particularly in South Asians), higher postprandial glucose excursions (resulting from carbohydrate-rich diets) and a greater risk of renal complications[3,4,7]. Furthermore, the incretin effect – postprandial amplification of insulin secretion by gastrointestinal peptide hormones – might not be blunted in East Asians with type 2 diabetes mellitus as it is in other ethnicities[8]. Given these potential differences, and the historical underrepresentation of Asians in clinical trials[9], there is a need for studies of glucose-lowering drugs focused on people with type 2 diabetes mellitus from Asia[4].

Achieving glycemic control early in the natural history of type 2 diabetes mellitus is likely to be as important for Asians as for other populations in preventing disease-related complications. The landmark United Kingdom Prospective Diabetes Study showed that achieving glycemic control early in the course of type 2 diabetes mellitus reduces the risk of microvascular complications, and might also have a longer-term beneficial impact on the risk of cardiovascular disease[10,11]. In the Kumamoto study, intensive insulin therapy lowered the risk for development of microvascular complications in Japanese patients with type 2 diabetes mellitus[12]. In people newly diagnosed with type 2 diabetes mellitus who are notably hyperglycemic; that is, they have a glycated hemoglobin A1c (HbA1c) level of ≥9%, monotherapy with any oral glucose-lowering drug is unlikely to achieve evidence-based glycemic goals (usually HbA1c <7.0%). Consequently, the current position statement from the American Diabetes Association and the European Association for the Study of Diabetes suggests initial combination therapy for individuals with HbA1c ≥9.0%[13,14], whereas the current International Diabetes Federation guideline states that initial combination therapy might be indicated if monotherapy is unlikely to achieve glycemic targets[15].

An increasing number of oral glucose-lowering drugs are available to combine with the usual first-line treatment of metformin. Guidelines generally recommend tailoring glucose-lowering treatment to the characteristics of the individual concerned[13,15]. Of note, incretin-based drugs – glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors – appear to be more efficacious in East Asians than in other ethnicities[16]. The combination of a DPP-4 inhibitor with metformin comprises two oral agents whose glucose-lowering effects are weight-neutral, with low intrinsic risk of hypoglycemia[14,17]. However, few clinical trials have evaluated an initial combination of metformin and a DPP-4 inhibitor (or any other oral glucose-lowering drug) exclusively in newly diagnosed patients with marked hyperglycemia. An exception is a recent multinational randomized study that investigated the initial combination of metformin and linagliptin, a DPP-4 inhibitor that – in contrast to most other members of this drug class – does not require dose adjustment for patients with chronic kidney disease[18–20]. In this recent study, the initial combination of metformin and linagliptin elicited substantial improvements in glycemic control from a mean baseline HbA1c of 9.8%, and was associated with a low incidence of hypoglycemia, weight gain or other adverse effects; importantly, treatment efficacy was unaffected by characteristics such as baseline HbA1c, age, BMI or renal function[21,22]. Given potential differences in pathophysiology and dietary habits, it is unclear whether these findings also apply to Asian patients. Hence, we report data for the cohort from Asian countries in this study.

METHODS

This was a post-hoc subgroup analysis of a 24-week, randomized, double-blind clinical trial carried out between January 2012 and April 2013 in 11 countries, including six in Asia (India, Israel, Malaysia, the Philippines, Sri Lanka and Thailand; ClinicalTrials.gov, NCT01512979).

The methodology of this clinical trial has previously been described[21]. In brief, individuals aged at least 18 years who were newly diagnosed with type 2 diabetes mellitus, had not previously received glucose-lowering pharmacotherapy, and had HbA1c levels between 8.5–12.0% were randomized to receive oral treatment with either linagliptin 5 mg once daily and metformin twice daily (uptitrated to 2,000 mg/day maximum) or linagliptin monotherapy for 24 weeks. The main exclusion criteria included impaired hepatic function, moderate-to-severe kidney disease (creatinine clearance <60 mL/min, by the Cockcroft–Gault equation) or a recent cardiovascular event. All eligible individuals provided written informed consent before participating. The protocol for the present clinical trial was approved by the independent ethics committees or institutional review boards of all participating centers, and the trial itself was carried out according to the Declaration of Helsinki and Good Clinical Practice defined by the International Conference on Harmonisation Harmonised Tripartite Guideline.

The subgroup analysis reported here pooled data for participants in this clinical trial from the six Asian countries; non-Asian individuals were included if they resided in these countries. The primary end-point was defined as the change from baseline in HbA1c after 24 weeks of treatment. Secondary end-points included the percentage of participants achieving HbA1c <7.0% after 24 weeks, change from baseline in fasting

plasma glucose after 24 weeks and change from baseline in bodyweight after 24 weeks. An additional secondary end-point comprised the percentage of participants who achieved a composite of HbA1c <7.0% after 24 weeks, with no episodes of hypoglycemia and no increase in bodyweight (defined as change in bodyweight from baseline of >1 kg). Safety analyses included the incidence and intensity of reported adverse events, which were classified using the Medical Dictionary for Regulatory Activities version 16.0. Hypoglycemia was defined as an investigator-reported episode of blood glucose ≤70 mg/dL (3.9 mmol/L) or an episode requiring the assistance of another person to administer carbohydrate, glucagon or other resuscitative action; the latter type of episode was defined as severe hypoglycemia.

The change in HbA1c from baseline to week 24 was evaluated in the full analysis set (FAS): all randomized participants who received ≥1 dose of the study drug and had a baseline HbA1c measurement and ≥1 on-treatment HbA1c measurement; the last observation carried forward was used to impute missing data. A sensitivity analysis evaluated the change in HbA1c from baseline to week 24 in the per-protocol completers' cohort (PPCC); the PPCC was defined as all randomized participants who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue therapy and had an HbA1c measurement at week 24. For the analysis of both the FAS and the PPCC, an analysis of covariance (ANCOVA) model was used that included treatment as a fixed effect and baseline HbA1c as a linear covariate. The two-sided *P*-value and the 95% confidence interval (CI) of the treatment difference (linagliptin/metformin minus linagliptin) were used to test for superiority of the linagliptin/metformin combination compared with linagliptin monotherapy. Change from baseline in HbA1c over time was evaluated for the FAS using a mixed model for repeated measurements that included treatment, continuous baseline HbA1c, week repeated within participant, week by baseline HbA1c interaction and week by treatment interaction; data available (observed cases) were used. HbA1c changes by baseline HbA1c category (<9.5% or ≥9.5%), baseline BMI category (<25, 25 to <30, 30 to <35, ≥35 kg/m^2), baseline age category (<35, 35 to <50, 50 to <65, ≥65 years) and baseline albuminuria category (urinary albumin-to-creatinine ratio </≥30 mg/g) were analyzed as previously described[22]. Similarly, change in fasting plasma glucose from baseline to week 24, and odds ratios for achievement of HbA1c <7.0% and the composite end-point in the FAS were analyzed as previously described[21,22]. Adverse events were analyzed with descriptive statistics for the treated set (all randomized participants who received ≥1 dose of study medication).

RESULTS

Baseline demographic and clinical characteristics

Of the 316 individuals in the treated set of the overall study population[21], 125 were from the Asian countries described (linagliptin/metformin, *n* = 62; linagliptin, *n* = 63). Of these participants, the FAS and PPCC comprised 115 (linagliptin/metformin, *n* = 58; linagliptin, *n* = 57) and 92 individuals (linagliptin/metformin, *n* = 50; linagliptin, *n* = 42), respectively. Participants were newly diagnosed, treatment-naïve and had marked hyperglycemia (Table 1). At baseline, the demographic and clinical characteristics of the participants were similar in the linagliptin/metformin and linagliptin groups (Table 1). Overall, the mean age was 48.7 years, mean HbA1c was 10.0% and mean BMI was 26.5 kg/m^2. Approximately 38% of participants had mild renal impairment.

Efficacy

Dose adjustment of metformin might be required for patients with kidney disease, depending on the degree of renal impairment[23]. By the end of the titration period, one (1.6%), six (9.7%) and 55 (88.7%) participants in the linagliptin/metformin group were taking 1,000 mg, 1,500 mg or 2,000 mg of metformin daily, respectively. The adjusted mean ± standard error (SE) change in HbA1c from baseline after 24 weeks in the FAS (last observation carried forward) was −2.99 ± 0.18% in the linagliptin/metformin group and −1.84 ± 0.18% in the linagliptin group, a treatment difference of −1.15% (95% CI −1.65 to −0.66, $P < 0.0001$). These glycemic changes were similar to those in the overall study population (comprising participants from Asian and non-Asian countries), in which the adjusted mean change in HbA1c after 24 weeks was −2.72% and −1.80% in the linagliptin/metformin and linagliptin groups, respectively (treatment difference of −0.79%; 95% CI −1.13 to −0.46, $P < 0.0001$)[21]. In the sensitivity analysis of the PPCC, the adjusted mean ± SE change in HbA1c from baseline after 24 weeks was −3.20 ± 0.15% in the linagliptin/metformin group and −2.09 ± 0.17% in the linagliptin group, a treatment difference of −1.11% (95% CI −1.56 to −0.66, $P < 0.0001$). The difference between the linagliptin/metformin and linagliptin groups in change in HbA1c from baseline was evident from week 6 onwards (Figure 1). Change in HbA1c from baseline was greater in participants with baseline HbA1c ≥9.5% than in those with baseline HbA1c <9.5% ($P = 0.0204$; Figure 2), but the effect of treatment was not significantly altered by baseline HbA1c ($P = 0.3456$). Reduction from baseline in HbA1c was not affected by baseline BMI ($P = 0.9281$ for effect of BMI; $P = 0.9092$ for interaction between BMI and treatment effect), baseline age ($P = 0.7915$ for effect of age; $P = 0.1792$ for interaction between age and treatment effect) or presence of albuminuria ($P = 0.1578$ for effect of albuminuria; $P = 0.7117$ for interaction between albuminuria and treatment effect).

HbA1c <7.0% after 24 weeks of treatment was achieved by significantly more linagliptin/metformin-treated participants (60.3%) than linagliptin-treated participants (21.1%; odds ratio 5.76, 95% CI 2.49 to 13.37, $P < 0.0001$). At week 24, the adjusted mean change ± SE from baseline in fasting plasma glucose was −58.5 ± 5.6 mg/dL with linagliptin/metformin and −31.1 ± 5.7 mg/dL with linagliptin, a treatment difference of

Table 1 | Baseline demographic and clinical characteristics (treated set)

	Linagliptin/ metformin (n = 62)	Linagliptin (n = 63)
Age, years (SD)	48.8 (10.0)	48.6 (9.1)
Female, *n* (%)	38 (61.3)	36 (57.1)
Race, *n* (%)		
Asian	57 (91.9)	61 (96.8)
White	5 (8.1)	1 (1.6)
Other†	0.0	1 (1.6)
Ethnicity, *n* (%)		
Non-Hispanic/Latino	61 (98.4)	63 (100.0)
Hispanic/Latino	1 (1.6)	0 (0.0)
Diabetes duration <1 year, *n* (%)	62 (100.0)	61 (96.8)‡
Mean HbA1c, % (SD)§	9.99 (1.30)	10.06 (1.06)
HbA1c, *n* (%)§		
<9.5%	20 (34.5)	18 (31.6)
≥9.5%	38 (65.5)	39 (68.4)
Mean fasting plasma glucose, mg/dL (SD)§	187.5 (48.1)	194.9 (53.4)
Mean BMI, kg/m^2 (SD)	26.50 (4.13)	26.42 (4.41)
BMI, *n* (%)		
<25 kg/m^2	26 (41.9)	27 (42.9)
25 to <30 kg/m^2	28 (45.2)	26 (41.3)
≥30 kg/m^2	8 (12.9)	10 (15.9)
Renal function (eGFR, mL/min/1.73 m^2, according to MDRD), *n* (%)		
Normal (≥90)	37 (59.7)	38 (60.3)
Mild impairment (60 to <90)	23 (37.1)	25 (39.7)
Moderate impairment (30 to <60)	2 (3.2)	0 (0.0)
Severe impairment (<30)	0.0	0.0
Microvascular disease, *n* (%)¶	9 (14.5)	12 (19.0)
Retinopathy	1 (1.6)	2 (3.2)
Nephropathy	1 (1.6)	1 (1.6)
Neuropathy	8 (12.9)	9 (14.3)
Macrovascular disease, *n* (%)¶	24 (38.7)	24 (38.1)
Coronary artery disease	0.0	0.0
Peripheral artery disease	3 (4.8)	1 (1.6)
Cerebrovascular disease	1 (1.6)	2 (3.2)
Hypertension	23 (37.1)	23 (36.5)
Concomitant medication, *n* (%)¶	31 (50.0)	34 (54.0)
Aspirin	5 (8.1)	3 (4.8)
Antihypertensive drugs	23 (37.1)	20 (31.7)
Lipid-lowering drugs	15 (24.2)	14 (22.2)

†Native American/Alaskan, Black/African American, Hawaiian/Pacific Islander. ‡For two linagliptin-treated participants, the time since diagnosis of type 2 diabetes mellitus was ≥12 months at screening. §Full analysis set (linagliptin/metformin n = 58; linagliptin n = 57). ¶Participants might be included in >1 subcategory. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; MDRD, Modification of Diet in Renal Disease Equation; SD, standard deviation.

–27.4 mg/dL (95% CI –43.3 to –11.5, P = 0.0009). The adjusted mean change ± SE in bodyweight after 24 weeks was –0.45 ± 0.41 kg in the linagliptin/metformin group and 1.33 ± 0.45 kg in the linagliptin group, a treatment difference

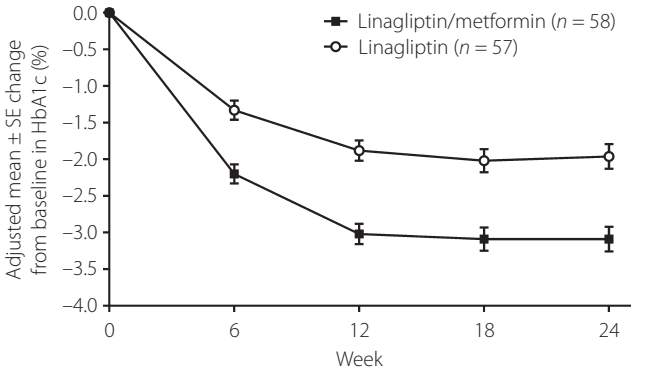

Figure 1 | Change from baseline in glycated hemoglobin A1c (HbA1c) over time in the full analysis set. SE, standard error.

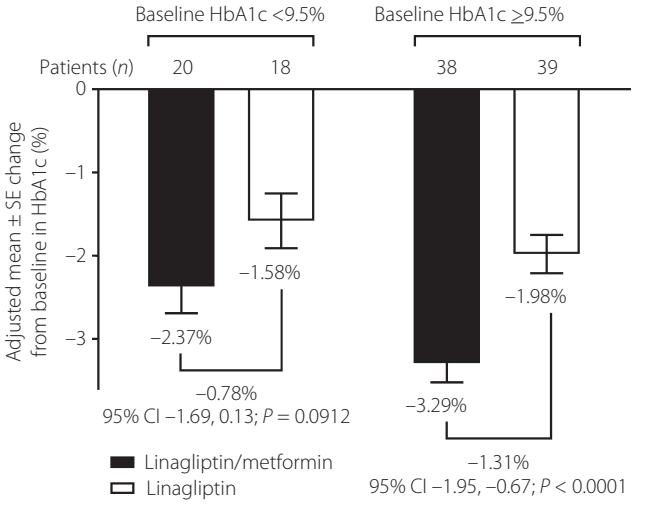

Figure 2 | Change from baseline in glycated hemoglobin A1c (HbA1c) after 24 weeks in the full analysis set by baseline HbA1c. CI, confidence interval; SE, standard error.

of –1.78 kg (95% CI –2.99 to –0.57, P = 0.0043). The composite end-point (HbA1c <7.0% at week 24, no hypoglycemia, no weight gain) was achieved by significantly more participants in the linagliptin/metformin group (46.6%) than in the linagliptin group (10.5%; Figure 3).

Safety and tolerability

The safety profiles of the treatment regimens in the participants from Asian countries were consistent with those seen in the overall study population[21]. No deaths occurred. The majority of participants reported adverse events (71.0% and 63.5% of the linagliptin/metformin and linagliptin groups, respectively), but few were considered drug-related by the investigators (9.7% and 4.8% of participants, respectively), and even fewer led to

treatment discontinuation (0% and 1.6%, respectively; Table 2). Serious adverse events were reported by one participant (1.6%) in each group. Of the adverse events that were prespecified as being of special interest, hepatic adverse events occurred in two (3.2%) and three (4.8%) participants in the linagliptin/metformin and linagliptin groups, respectively, and hypersensitivity reactions occurred in one (1.6%) and two (3.2%) participants in the linagliptin/metformin and linagliptin groups, respectively; there were no cases of pancreatitis, renal adverse events or severe cutaneous reactions. Gastrointestinal disorders occurred in 12.8% of participants (linagliptin/metformin 12.9%; linagliptin 12.7%), none of whom discontinued treatment as a result of such episodes. Hypoglycemia occurred in 6.5% of participants receiving linagliptin/metformin and 4.8% of those receiving linagliptin; none of the episodes were severe (i.e., required assistance from another person). The other most common adverse events in the linagliptin/metformin group were dyslipidemia (11 participants [17.7%]), urinary tract infection (six participants [9.7%]), and headache, back pain and hypertension (four participants [6.5%] each; Table 2). There were no cases of pancreatic cancer or heart failure.

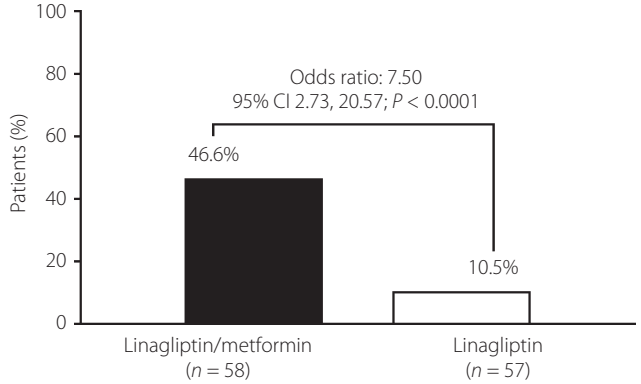

Figure 3 | Percentage of participants achieving a composite end-point of glycated hemoglobin A1c (HbA1c) <7.0% at week 24 with no episodes of investigator-reported hypoglycemia and no weight gain (change in bodyweight from baseline of >1 kg).

Table 2 | Summary of adverse events over 24 weeks (treated set)

Patients (%)	Linagliptin/ metformin (*n* = 62)	Linagliptin (*n* = 63)
Any adverse event	71.0	63.5
Drug-related adverse event	9.7	4.8
Serious adverse event	1.6	1.6
Death	0.0	0.0
Requiring hospitalization	1.6	1.6
Adverse event leading to discontinuation	0.0	1.6
Adverse events of special interest†		
Hepatic adverse events	3.2	4.8
Hypersensitivity reactions	1.6	3.2
Gastrointestinal disorders‡	12.9	12.7
Adverse events with an incidence >5.0% in either group§		
Dyslipidemia	17.7	30.2
Urinary tract infection	9.7	12.7
Headache	6.5	4.8
Hypoglycemia¶	6.5	4.8
Back pain	6.5	3.2
Hypertension	6.5	0.0
Upper respiratory tract infection	4.8	7.9
Hyperglycemia	3.2	12.7

†Pancreatitis, renal adverse event, hepatic adverse event, hypersensitivity reaction or severe cutaneous reaction. ‡System organ class from the Medical Dictionary for Regulatory Activities, version 16.0 (MedDRA). §Preferred terms from MedDRA. ¶Includes asymptomatic hypoglycemia, which was not reported as an adverse event; the incidence of symptomatic hypoglycemia alone was 1.6% with linagliptin/metformin and 4.8% with linagliptin.

DISCUSSION

Historically, most participants in clinical trials of glucose-lowering drugs for type 2 diabetes mellitus have been from Western countries. Given the current epidemic of type 2 diabetes mellitus in Asia, and interethnic differences in pathophysiology and lifestyle factors both within Asian regions and compared with Caucasian populations – including incretin physiology and pathophysiology[8] – there is a need for data from clinical trials of patients in Asia to inform treatment choices[4]. In the subgroup analysis reported here, the initial combination of metformin and linagliptin elicited substantial reductions in hyperglycemia in newly diagnosed patients from Asia, and was associated with a low incidence of associated hypoglycemia, weight gain or other side-effects. The magnitude of the reduction from baseline in HbA1c was not affected by BMI or age. Despite marked hyperglycemia at baseline (mean HbA1c 10.0%), almost two-thirds of the participants (60%) receiving the linagliptin/metformin combination achieved glycemic control, defined as HbA1c <7.0%. This finding is noteworthy, as the widely accepted HbA1c target of 7.0%[13,15] is derived largely from the United Kingdom Prospective Diabetes Study, which also enrolled newly diagnosed individuals. In the United Kingdom Prospective Diabetes Study, early achievement of HbA1c <7.0% significantly reduced the risk for microvascular complications of type 2 diabetes mellitus, as well as the longer-term risk of cardiovascular events and premature death[10,11]. Evidence for targeting HbA1c <7.0% in Asians comes from the Kumamoto study, in which Japanese patients treated with insulin to a mean HbA1c of 7.1% had a significantly lower risk for microvascular complications than those receiving less intensive therapy who only achieved HbA1c 9.4%[12]. Also notable in the present analysis was that almost half the participants in the linagliptin/metformin group not only achieved HbA1c <7.0%, but did so without experiencing weight gain or any episodes of hypoglycemia. Overall, these findings are consistent with the efficacy and safety profiles of linagliptin/metformin and

linagliptin seen in the parent study, which also included individuals from Europe and North America[21].

Thus, the current analysis supports the use of oral combination treatments for newly diagnosed Asian patients with marked hyperglycemia. Current guidelines for initial treatment of type 2 diabetes mellitus in China[24], India[25] and Japan[26] suggest to begin with oral monotherapy but consider insulin for individuals with marked hyperglycemia, defined as HbA1c ≥9.0% by the Chinese Diabetes Society[24]. Oral combination therapy is identified by Western guidelines as an alternative for newly diagnosed patients with marked hyperglycemia[13–15].

Linagliptin has previously shown efficacy and tolerability in Asians with type 2 diabetes mellitus[27–34]. However, the reductions in hyperglycemia in the present analysis were notably larger than in these previous studies. The high baseline levels of HbA1c in the current analysis are likely to be one reason for this difference[35–37]. The magnitude of the glycemic response also suggests that oral combination treatment for newly diagnosed patients with marked hyperglycemia can be particularly effective when relevant pathophysiological processes are targeted. Asian patients, who often have substantial β-cell dysfunction, might respond well to insulinotropic agents, such as DPP-4 inhibitors, that do not cause hypoglycemia. Additionally, incretin therapies, including DPP-4 inhibitors, elicit much of their antihyperglycemic effect through reducing postprandial glucose excursions[38], which are generally high in Asian patients as a consequence of carbohydrate-rich diets[39]. Taken together, these pathophysiological characteristics might, at least partly, explain the apparently greater glucose-lowering effects of DPP-4 inhibitors in Asians – particularly East Asians[16] – than in other ethnic groups[40]. Although postprandial glucose levels were not evaluated in the current study, a pooled analysis of data from global clinical trials showed that linagliptin might elicit significant reductions in postprandial glucose excursions in Asian patients[29]. Combining a DPP-4 inhibitor with metformin might complement this effect, as metformin mainly reduces fasting plasma glucose[14]. Notably, however, despite potential pathogenetic differences and dietary habits of Asian patients, the results of the present analysis are similar to those seen in the overall study population[22]. This might reflect the lack of East Asian patients in the study.

Although the participants in this study were newly diagnosed with type 2 diabetes mellitus, almost 40% already had mild renal impairment. The presence of kidney disease influences treatment choice, as nearly all glucose-lowering drugs are excreted by the kidneys and, therefore, are either contraindicated or require dose adjustment to avoid adverse effects resulting from increased drug exposure[14]. In the present study, the dose of linagliptin was not adjusted for individuals with renal impairment, based on the current prescribing information for this drug[18] and its pharmacokinetic profile in Asians[41].

The safety and tolerability of glucose-lowering treatment is an important consideration, particularly for newly diagnosed patients, as it might affect their long-term adherence to therapy. In the present study, few participants experienced drug-related adverse events, including hypoglycemia, and none had severe episodes of hypoglycemia. The similar incidence of gastrointestinal disorders between treatment groups might be a chance finding resulting from the low number of events (just eight individuals in each group). This was also seen in the parent study[21].

The strengths and limitations of the current study are important considerations when interpreting its findings. One major limitation is its post-hoc subgroup nature, which is potentially subject to confounding factors. Thus, the present results need to be interpreted with caution. However, the findings are consistent with the efficacy observed in dedicated clinical trials of linagliptin in Asians with type 2 diabetes mellitus[27–34], albeit with larger reductions in HbA1c, as discussed above. Another important limitation is the lack of participants from East Asia, which restricts the generalizability of the results across the entire Asian region. However, the findings are in concordance with previous studies of the linagliptin/metformin combination, including a clinical trial in East Asian patients[27]. Additionally, linagliptin monotherapy was previously shown to be efficacious and well tolerated in newly diagnosed, moderately hyperglycemic Chinese patients (mean baseline HbA1c 8.0%)[34]. Other limitations of the current analysis include its small sample size, lack of data on pancreatic β-cell function, and the possibility that dietary and exercise interventions might have contributed to the glycemic reductions, although the minimal changes in bodyweight suggest that the effects of lifestyle modification were not substantial. An additional consideration is that participants were included based on country of residence, not ethnicity; thus, a small number were of non-Asian ethnicity (seven [5.6%]).

In conclusion, the combination of metformin and linagliptin substantially improved glycemic control and was well tolerated in Asians newly diagnosed with type 2 diabetes mellitus who had marked hyperglycemia. In many individuals, this improvement in glycemia was achieved without weight gain or hypoglycemia. These findings could aid clinical decision-making, as they suggest that Asians with newly diagnosed type 2 diabetes mellitus and marked hyperglycemia can be effectively treated with initial combinations of oral glucose-lowering medications.

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DISCLOSURE

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