Efficacy and Safety of Linagliptin in 2681 Asian Patients Stratified by Age, Obesity, and Renal Function: A Pooled Analysis of Randomized Clinical Trials

Guang Ning, Tushar Bandgar, Uwe Hahnke, Jisoo Lee, Juliana C. N. Chan

ABSTRACT

Introduction: Asian patients with type 2 diabetes (T2D) are younger, leaner, and more likely to develop renal dysfunction than White populations. In this multiethnic analysis of data from phase 3 trials, we investigated the efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin in Asians stratified by these subphenotypes.

Methods: Data from randomized, double-blind, placebo-controlled trials evaluating linagliptin (as monotherapy, add-on therapy to metformin ± sulfonylurea, combined with pioglitazone or added to insulin) were pooled with efficacy data from 11 randomized trials of at least 24 weeks and safety data from 15 trials of various durations.

Results: In the efficacy set, 1404 Asian patients received linagliptin [mean (standard deviation) age 54.5 (10.1) years; body mass index (BMI) 26.0 (3.9) kg/m^2] and 661 received placebo [age 55.0 (9.7) years; BMI 26.1 (3.9) kg/m^2] with the same glycated hemoglobin (HbA1c): 8.2 (0.9)% in both groups. At 24 weeks, the placebo-corrected adjusted mean ± standard error change from baseline in HbA1c with linagliptin was -0.73 ± 0.04% (95% confidence interval -0.81, -0.65; P < 0.0001). Reductions in HbA1c were similar upon stratification by age (<65 years, -0.71 ± 0.05% (P < 0.0001); ≥65 years, -0.81 ± 0.10% (P < 0.0001)), BMI (<25 kg/m^2, -0.82 ± 0.06% (P < 0.0001); ≥25 kg/m^2, -0.65 ± 0.06% (P < 0.0001)) and estimated glomerular filtration rate (<90 mL/min/1.73 m^2, -0.71 ± 0.06% (P < 0.0001); ≥90 mL/min/1.73 m^2, -0.75 ± 0.06% (P < 0.0001)). In the safety set (linagliptin, n = 1842; placebo, n = 839),
52.2% and 54.6% of patients, respectively, experienced adverse events. The rates of drug-related adverse events were 10.9% in the linagliptin group and 10.4% in the placebo group. The respective rates of hypoglycemia were 8.3% and 9.5%, mainly among patients treated with sulfonylurea or insulin. Severe hypoglycemia was rare (<1.0% in either group).

**Conclusion:** Linagliptin effectively reduced hyperglycemia in Asian patients with uncontrolled T2D, irrespective of age, BMI, renal function, or ethnic subgroups, and was well tolerated.

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**Keywords:** Asian patients; Data pooling; Efficacy; Ethnic groups; Linagliptin; Type 2 diabetes; Safety

**INTRODUCTION**

Asia has experienced a marked rise in the prevalence of type 2 diabetes (T2D) in recent years [1, 2]. Countries such as India and China have undergone rapid economic development with dietary and lifestyle changes resulting in obesity which has unmasked a genetic predisposition for T2D [3]. If left unchecked, the diabetic population is predicted to rise from 72.1 million in 2013 to 123 million by 2035 in Southeast Asia alone with major socioeconomic and healthcare implications [1]. Asian patients exhibit phenotypic profiles different from Western populations including young age of diagnosis and propensity for renal disease [3–6]. Given the long disease duration, high risk for renal disease, and importance of glucose control for renoprotection, early intervention with new glucose-lowering therapies with few side effects (e.g., hypoglycemia, weight gain) may be particularly relevant to Asian patients with T2D [3]. With increasing numbers of Asian patients participating in clinical trials, pooled analysis of these data may inform clinical practice [7].

Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong the half-life of the incretin hormone, glucagon-like peptide-1 (GLP1), which augments prandial insulin secretion and suppresses glucagon secretion [8]. Linagliptin is a potent and selective DPP-4 inhibitor with a predominately non-renal route of elimination and does not require dose adjustment [9]. In multinational phase 3 trials, linagliptin 5 mg once daily compared with placebo improved glycemic control without weight gain or an increased risk for hypoglycemia [10–13]. Dedicated trials in different ethnic populations confirmed the efficacy and safety of linagliptin in Japanese [14], Chinese [15], and Asian [16, 17] patients with T2D. In a pooled data analysis from phase 3 clinical trials, linagliptin improved glycemic control in Asian patients with T2D (4 trials; n = 1029), which was well tolerated (10 trials; n = 1477) [18].

In this study, we expanded the aforementioned pooled analysis using data from 15 phase 3 trials of linagliptin including subanalysis stratified by ethnicity, BMI, age, and renal function.

**METHODS**

**Study Design and Patient Population**

This was a retrospective analysis of patient-level data that was pooled from randomized, double-blind, placebo-controlled phase 3 clinical trials comparing linagliptin versus placebo as monotherapy or in combination with other glucose-lowering drugs. The analysis included subpopulations of Asian patients from 15 trials lasting for 12–52 weeks (Table 1) recruited from East Asia (China, Korea, Taiwan, Japan); Southeast Asia (Indonesia, Malaysia, Philippines, Singapore, Thailand); South Asia (India).

The study design and enrollment criteria for the 15 trials were similar, with enrollment of treatment-naïve or treatment-exposed patients with T2D. All patients were at least 18 years of age and had a BMI of ≤40 kg/m². The glycated hemoglobin (HbA1c) levels ranged from 7.0% to 11.0% in treatment-naïve patients or from 6.5% to 10.5% in treatment-exposed patients. Exclusion criteria included impaired hepatic function (serum alanine transaminase, aspartate transaminase, or alkaline phosphatase levels more than three times the upper limit of normal); recent occurrence of myocardial
| Reference | Patient population | Treatment regimen | Duration (weeks) | Drug-naïve or add-on to existing glucose-lowering therapy | Age(s) (years) | Registration number |
|-----------|--------------------|-------------------|-----------------|--------------------------------------------------------|----------------|-------------------|
| [50]      | Thai et al.        | Add-on to metformin | 22              | Add-on to metformin                                   | 18–80          | NCT00752702       |
| [49]      | Bantner et al.     | Add-on to metformin | 3               | Add-on to metformin                                   | 18–70          | NCT01050095       |
| [48]      | Ross et al.        | Add-on to metformin + pioglitazone | 12 | Add-on to metformin (2.5 mg bid vs 5 mg) | 18–80          | NCT01050237       |
| [47]      | Bajaj et al.       | Initial combination with metformin | 12 | Initial combination with metformin + pioglitazone | 18–80          | NCT00966588       |
| [46]      | Hahn et al.        | Initial combination with metformin | 45  | Initial combination with metformin + pioglitazone | 18–80          | NCT1869161        |
| [45]      | McCall et al.      | Add-on to metformin | 6               | Add-on to metformin                                   | 18–60          | NCT08008000       |
| [44]      | Vukich et al.      | Add-on to metformin | 83              | Add-on to metformin                                   | 18–70          | NCT00966588       |
| [43]      | Leem et al.        | Add-on to metformin | 21              | Add-on to metformin                                   | 18–70          | NCT00966588       |
| [42]      | Kawai et al.       | Add-on to metformin | 60              | Add-on to metformin                                   | 18–70          | NCT00966588       |
| [41]      | Kawamori et al.    | Drug-naïve or add-on to existing glucose-lowering therapy | 199 | Drug-naïve or add-on to existing glucose-lowering therapy | 18–70          | NCT00966588       |
| [40]      | Overt et al.       | Add-on to metformin | 45              | Add-on to metformin                                   | 18–80          | NCT00966588       |
| [39]      | Takahara et al.    | Add-on to metformin | 35              | Add-on to metformin                                   | 18–80          | NCT00966588       |
| [38]      | Delli Piane et al. | Initial combination with metformin | 115 | Initial combination with metformin + pioglitazone | 18–80          | NCT00966588       |
| [37]      | Combs et al.       | Initial combination with metformin | 33              | Initial combination with metformin + pioglitazone | 18–80          | NCT00966588       |

Table 1. Randomized, double-blind, placebo-controlled trials included in this pooled analysis.
infarction, stroke, or transient ischemic attack; any requirement for hemodialysis and kidney transplantation.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all trial participants.

**Efficacy and Safety Assessments**

Efficacy data were pooled from 11 randomized trials of at least 24 weeks’ duration (Table 1). The primary efficacy variable was the mean change from baseline at week 24 in HbA1c. Secondary endpoints included the mean change from baseline at week 24 in HbA1c by subgroups of region (East Asia, Southeast Asia, South Asia), BMI ($<25$ or $\geq 25$ kg/m$^2$), and age ($<65$ or $\geq 65$ years); the mean change from baseline at week 24 in fasting plasma glucose (FPG); the mean change from baseline in HbA1c and FPG levels over time; the mean change from baseline after 24 weeks in incremental postprandial glucose (IPPG) levels.

Safety data were pooled from 15 trials (including the 11 trials from the efficacy set) of various durations to allow the broadest possible detection of adverse events. Safety assessments included the frequency and intensity of adverse events, including hypoglycemia, as coded by the Medical Dictionary for Regulatory Activities (MedDRA, version 16.0). Investigator-reported hypoglycemic events were defined as a blood glucose level of 3.9 mmol/L or less, with or without symptoms; severe hypoglycemia was defined as needing assistance from another person to administer resuscitative actions, irrespective of blood glucose concentration. The incidence of hypoglycemia was also analyzed according to whether or not patients were receiving sulfonylurea and/or insulin background therapies.

**Statistical Analysis**

Efficacy assessments were conducted on the full analysis set (FAS), which comprised all

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### Table 1

| ClinicalTrials.gov registration number | Patient population | Treatment regimen | Duration (weeks) | Treatment regimen | Patient population | Duration (weeks) | References |
|---------------------------------------|--------------------|-------------------|-----------------|-------------------|--------------------|-----------------|------------|
| NCT01215097                           | Aged 18–80 years; Asian patients | Add-on therapy to metformin | 24              | Linagliptin       | 205                | 100             | Wang et al. [17] |
| NCT01214239                           | Aged 18–80 years; Asian patients | Monotherapy       | 24              | Placebo           | 200                | 99              | Chen et al. [16] |
| NCT01214239                           | Aged 18–80 years; Asian patients | Add-on therapy to metformin | 24              | Linagliptin       | 205                | 100             | Wang et al. [17] |

*a* Study included in the previous pooled analysis by Zeng et al. [18]

*b* The study duration was a total of 52 weeks: an initial 12-week placebo-controlled phase was followed by a 14-week active-controlled phase and then a final 26-week open-label extension phase. Data shown are from patients receiving linagliptin 5 mg or placebo in the initial 12-week phase.
randomized patients treated with at least one dose of study drug and who had a baseline and at least one on-treatment HbA1c measurement. The mean change in HbA1c from baseline to week 24 was compared between the linagliptin and placebo groups in the pooled population using an analysis of covariance (ANCOVA). The model included the terms “treatment”, “baseline HbA1c”, “prior oral antidiabetes drugs (OADs; yes/no)”, and “individual study”. A last observation carried forward (LOCF) approach was used to replace missing data.

Secondary efficacy endpoints were analyzed using the FAS. Mean change in HbA1c from baseline after 24 weeks by Asian regional sub-populations and by ≥65 years age group were analyzed using ANCOVA similar to the primary analysis. Mean change in HbA1c from baseline after 24 weeks by BMI category (<25 kg/m², ≥25 mg/m²) was analyzed using ANCOVA similar to the primary analysis, and with the same terms as the primary analysis model plus the term “BMI category (<25, ≥25 kg/m²)”. The mean change in FPG from baseline to week 24 was compared between the linagliptin and placebo groups using an ANCOVA similar to the primary analysis with a LOCF approach, and with the same terms as the primary analysis model plus “baseline FPG”. Mean changes in HbA1c and FPG levels over time were analyzed using descriptive statistics with missing data replaced using a LOCF approach. The mean change in iPPG from baseline after 24 weeks was compared between the linagliptin and placebo groups in a subset of patients who had undergone a meal tolerance test and who had available data (observed cases, OC) using ANCOVA similar to the primary analysis, and with the same terms as the primary analysis model plus the term “baseline iPPG”.

Exploratory analyses were carried out to determine the influence of the following factors or covariates on the adjusted mean change from baseline in HbA1c, “use of insulin”; “Asia sub-region”; “baseline BMI”. Regression and correlation analyses were used to investigate the relationship between baseline BMI and change from baseline in HbA1c at week 24.

Safety analyses were conducted on the treated set, which comprised all patients who were treated with at least one dose of study medication. Adverse events were summarized using descriptive statistics without any additional formal inferential statistical analysis.

RESULTS

Demographics and Clinical Characteristics at Baseline

The FAS (efficacy) population comprised 2065 Asian patients (linagliptin, \( n = 1404 \); placebo, \( n = 661 \)); the treated (safety) set comprised 2681 Asian patients (linagliptin, \( n = 1842 \); placebo, \( n = 839 \)) (Table 2). In the FAS, mean standard deviation (SD) age, HbA1c, and BMI were 54.7 (10.0) years, 8.2 (0.9)%, and 26.0 (3.9) kg/m², respectively. Most patients (59.0%) were from East Asia and half had the disease for more than 5 years. Approximately 50% had estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m², most of whom (43% of all patients) had mild renal impairment (eGFR, 60 to <90 mL/min/1.73 m²). Approximately 50% of patients were using two or more OADs at enrollment. The linagliptin and placebo groups had similar profiles, except for higher insulin use in the placebo group (14.1%) than in the linagliptin group (6.6%). Mean (SD) exposure to linagliptin was 185 (75) days and to placebo was 204 (105) days (median, 170 days in each group).

Efficacy

At 24 weeks, the adjusted mean ± standard error (SE) change from baseline in HbA1c was −0.77 ± 0.02% with linagliptin and −0.04 ± 0.03% with placebo, with a placebo-corrected difference of −0.73 ± 0.04% [95% confidence interval (CI) −0.81, −0.65; \( P < 0.0001 \)] (Supplementary Fig. S1). Linagliptin was superior to placebo in reducing HbA1c stratified by Asian regional subpopulation [East Asians, −0.68 ± 0.05% (95% CI −0.78, −0.58; \( P < 0.0001 \)); Southeast Asians, −0.90 ± 0.11% (95% CI −1.12, −0.68; \( P < 0.0001 \)); South Asians, −0.75 ± 0.11% (95% CI −0.96, −0.54;
### Table 2 Baseline demographics and clinical characteristics of the pooled population of Asian patients

|                          | Linagliptin | Placebo |
|--------------------------|-------------|---------|
| Patients (FAS<sup>a</sup>), n | 1404        | 661     |
| Male, n (%)              | 721 (51.4)  | 356 (53.9) |
| Age, years, mean (SD)    | 54.5 (10.1) | 55.0 (9.7) |
| Age group, n (%)         |             |         |
| ≤50 years                | 469 (33.4)  | 211 (31.9) |
| 51 to <65 years          | 696 (49.6)  | 342 (51.7) |
| 65 to <75 years          | 212 (15.1)  | 99 (15.0) |
| ≥75 years                | 27 (1.9)    | 9 (1.4) |
| Asian regions, n (%)     |             |         |
| East                     | 827 (58.9)  | 393 (59.5) |
| Southeast                | 190 (13.5)  | 94 (14.2) |
| South                    | 330 (23.5)  | 140 (21.2) |
| Centers outside of Asia  | 57 (4.1)    | 34 (5.1) |
| Body weight, kg, mean (SD)| 68.0 (12.7) | 68.6 (12.2) |
| BMI, kg/m<sup>2</sup>, mean (SD) | 26.0 (3.9) | 26.1 (3.9) |
| BMI, categorical, n (%)  |             |         |
| <25 kg/m<sup>2</sup>     | 617 (43.9)  | 295 (44.6) |
| 25 to ≤30 kg/m<sup>2</sup> | 597 (42.5)  | 275 (41.6) |
| ≥30 kg/m<sup>2</sup>     | 190 (13.5)  | 91 (13.8) |
| Renal function (eGFR, mL/min/1.73 m<sup>2</sup>, according to MDRD), n (%) | | |
| Normal (≥90)             | 710 (50.6)  | 305 (46.1) |
| Mild (60 to <90)         | 591 (42.1)  | 299 (45.2) |
| Moderate (30 to <60)     | 94 (6.7)    | 43 (6.5) |
| Severe or ESRD (<30)     | 9 (0.6)     | 14 (2.1) |
| HbA1c, %, mean (SD)      | 8.2 (0.9)   | 8.2 (0.9) |
| FPG, mg/dL, mean (SD)    | 154.7 (39.3) | 155.8 (40.4) |
| Time since diagnosis of diabetes, n (%) | | |
| ≤1 year                  | 302 (21.5)  | 135 (20.4) |
| >1 to ≤5 years           | 444 (31.6)  | 208 (31.5) |
| >5 years                 | 658 (46.9)  | 318 (48.1) |

### Table 2 continued

|                          | Linagliptin | Placebo |
|--------------------------|-------------|---------|
| Oral antidiabetes drugs at enrollment, n (%) | | |
| 0                        | 312 (22.2)  | 152 (23.0) |
| 1                        | 374 (26.6)  | 189 (28.6) |
| ≥2                       | 718 (51.1)  | 320 (48.4) |
| Insulin background therapy at screening, n (%) | | |
| No                       | 1312 (93.4) | 568 (85.9) |
| Yes                      | 92 (6.6)    | 93 (14.1) |
| Patients (TS<sup>b</sup>), n     | 1842        | 839     |
| Males, n (%)             | 984 (53.4)  | 475 (56.6) |
| Age, years, mean (SD)    | 55.1 (10.2) | 55.4 (10.0) |
| Age group, n (%)         |             |         |
| ≤50 years                | 596 (32.4)  | 255 (30.4) |
| 51 to <65 years          | 888 (48.2)  | 424 (50.5) |
| 65 to <75 years          | 321 (17.4)  | 147 (17.5) |
| ≥75 years                | 37 (2.0)    | 13 (1.5) |
| Body weight, kg, mean (SD)| 67.9 (12.7) | 68.2 (12.4) |
| BMI, kg/m<sup>2</sup>, mean (SD) | 25.9 (4.0) | 25.9 (4.0) |
| BMI, categorical, n (%)  |             |         |
| <25 kg/m<sup>2</sup>     | 837 (45.4)  | 392 (46.7) |
| 25 to ≤30 kg/m<sup>2</sup> | 747 (40.6)  | 337 (40.2) |
| ≥30 kg/m<sup>2</sup>     | 258 (14.0)  | 110 (13.1) |
| Renal function (eGFR, mL/min/1.73 m<sup>2</sup>, according to MDRD), n (%) | | |
| Normal (≥90)             | 859 (46.6)  | 355 (42.3) |
| Mild (60 to <90)         | 827 (44.9)  | 384 (45.8) |
| Moderate (30 to <60)     | 143 (7.8)   | 76 (9.1) |
| Severe or ESRD (<30)     | 13 (0.7)    | 24 (2.9) |
| HbA1c, %, mean (SD)      | 8.2 (0.9)   | 8.2 (0.9) |
| FPG, mg/dL, mean (SD)    | 156.1 (38.4) | 156.4 (40.6) |
| Time since diagnosis of diabetes, n (%) | | |
| ≤1 year                  | 347 (18.8)  | 154 (18.4) |
Table 2 continued

|                      | Linagliptin | Placebo |
|----------------------|------------|---------|
| >1 to ≤5 years       | 616 (33.4) | 276 (32.9) |
| >5 years             | 879 (47.7) | 409 (48.7) |

Oral antidiabetes drugs at enrollment, n (%)

- 0: 408 (22.1)
- 1: 621 (33.7)
- ≥2: 813 (44.1)

Insulin background therapy at screening, n (%)

- No: 1735 (94.2)
- Yes: 107 (5.8)

BMI body mass index, eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, FAS full analysis set, FPG fasting plasma glucose, HbA1c glycated hemoglobin, MDRD modification of diet in renal disease, SD standard deviation, TS treated set

- A: All patients who had a baseline and at least one on-treatment HbA1c measurement
- B: All patients who were treated with at least one dose of study medication

P < 0.0001; Fig. 1a], BMI categories [≤25 kg/m², −0.82 ± 0.06% (95% CI −0.94, −0.70; P < 0.0001]; >25 kg/m², −0.65 ± 0.06% (95% CI −0.76, −0.54; P < 0.0001); Fig. 1b], age categories [≤65 years, −0.71 ± 0.05% (95% CI −0.80, −0.62; P < 0.0001); >65 years, −0.81 ± 0.10% (95% CI −1.01, −0.60; P < 0.0001); Fig. 1c], and eGFR categories [≤90 mL/min/1.73 m², −0.71 ± 0.06% 95% CI (−0.82, −0.60; P < 0.0001); ≥90 mL/min/1.73 m², −0.75 ± 0.06% (95% CI −0.87, −0.64; P < 0.0001); Fig. 1d]. In our exploratory analysis, linagliptin tended to have greater efficacy in the Southeast Asian subpopulation, patients with BMI < 25 kg/m², and those ≥65 years compared with their comparative counterparts. Exploratory analyses showed that the adjusted mean HbA1c change from baseline in the overall population remained the same when each of the covariates “use of insulin”, “Asia subregion”, or “baseline BMI” was added separately to the ANCOVA model. No significant interaction was found when the interaction term of each of these covariates with treatment was added to the analysis model (Supplementary Table S1).

At week 24, the adjusted mean ± SE change from baseline in FPG in the pooled Asian population was −10.42 ± 0.93 mg/dL and 4.86 ± 1.36 with linagliptin and placebo, respectively, with a placebo-corrected difference of −15.28 mg/dL (95% CI −18.54, −12.03; P < 0.0001). The placebo-corrected differences in FPG levels for East Asia was −13.91 mg/dL (95% CI −18.12, −9.71; P < 0.0001); Southeast Asia, −13.48 mg/dL (95% CI −21.11, −5.84; P = 0.0006); South Asia, −17.69 mg/dL (95% CI −25.11, −10.26; P < 0.0001).

During the 24-week treatment period, the largest reductions occurred during the first 6–12 weeks and were maintained until week 24 (Supplementary Figs. S2a, b). In a subset of patients who underwent meal tolerance tests (n = 40), treatment with linagliptin improved iPPG (placebo-corrected mean change from baseline with linagliptin, −45.0 mg/dL; 95% CI −71.6, −18.4; P = 0.0014; Supplementary Fig. S3). Exploratory analyses showed that the adjusted mean change from baseline levels of iPPG in the overall population was not significantly affected by any of the evaluated covariates: “use of insulin”, “Asia subregion”, or “baseline BMI” (Supplementary Table S2). No clinically relevant increase in body weight was observed with linagliptin (data not shown).

Safety

Overall adverse events and drug-related adverse events occurred at similar frequencies with both treatments (Supplementary Table S3). Approximately 3% of patients in each group discontinued treatment because of adverse events. The frequency of serious adverse events was low and similar between the placebo and linagliptin groups (4.5% vs. 3.0%). One of these events was reported as life-threatening and possibly drug-related (acute myocardial infarction in the linagliptin group). No cases of pancreatitis or pancreatic cancer were reported in either treatment group. There was one death in the placebo group (acute myocardial infarction and

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cardiovascular death). After adjusting for time exposed to study drugs, the incidence rates were similar between the study groups (Supplementary Table S3).

The frequency of investigator-reported hypoglycemia with linagliptin was comparable to placebo (8.3% vs. 9.5%). Less than 1.0% of patients in either group experienced severe hypoglycemia (0.3% vs. 0.1%). More hypoglycemic events occurred among patients treated with sulfonylurea and/or insulin (Supplementary Fig. S4). Severe hypoglycemia was experienced by 0.6% of linagliptin and 0.3% of placebo patients treated with sulfonylurea and/or insulin and was not reported in patients receiving other background therapies.

In a subgroup analysis of elderly patients (≥65 years) treated with linagliptin (n = 358) or placebo (n = 160), 53.6% of the linagliptin group and 61.9% of placebo group reported an adverse event. Serious adverse events and drug-related adverse events were reported by 4.5% and 12.6% of the linagliptin group. The respective frequencies were 6.9% and 17.5% in the placebo group. The incidence of hypoglycemia in the linagliptin group was 9.5% versus 18.1% in the placebo group, mainly among patients treated with sulfonylurea and/or insulin.

**DISCUSSION**

In this pooled analysis, we have confirmed the efficacy and safety of linagliptin in an Asian multiethnic population, irrespective of BMI,
age, and renal function. Early age of diagnosis and therefore long disease duration as well as high risk for renal dysfunction in Asian T2D patients may have implications for the selection of antidiabetes drugs [3, 5, 6, 19, 20]. DPP-4 inhibitors augment prandial insulin secretion and suppress glucagon with low risk of hypoglycemia [21]. Meta-analysis suggested that Asians or subjects with low BMI had favorable response to DPP-4 inhibition [22, 23]. Given that beta-cell insufficiency is a prominent feature in Asian populations with T2D [24, 25], DPP-4 inhibitors can have therapeutic advantages over other drug classes in these patients.

In this pooled analysis of 11 trials, 24-weeks’ treatment with linagliptin reduced HbA1c by 0.7% after correction for placebo effect with reduction in both FPG and iPPG in the entire and subregional populations. Data from 15 trials also confirmed the low occurrence of adverse events and the risk of hypoglycemia was mainly limited to patients treated with sulfonylurea or insulin therapy. In elderly subjects aged ≥65 years, linagliptin reduced HbA1c by 0.8% with low risk of adverse events.

These results confirmed an earlier analysis of pooled Asian data from four studies [18]. Exploratory analyses such as pooled analyses reinforce the efficacy and safety findings of individual trials, improve the detection of adverse events that occur at low frequencies, and provide a larger database for performing subgroup and treatment interactions. In two phase 3 trials that exclusively recruited patients in China, Malaysia, and the Philippines [16, 17], which evaluated linagliptin as monotherapy [16] or as add-on to metformin [17] also confirmed the efficacy and safety of linagliptin. Consistent with the overall linagliptin phase 3 clinical development program, all these Asian trials included a significant proportion of patients with renal impairment in whom linagliptin was efficacious, safe, and well tolerated [26].

In a multiethnic population, Asian individuals had a lower insulinogenic index than White populations, which might contribute to the high prevalence of T2D in Asian populations [27]. Other researchers have reported a linear relationship between BMI and beta-cell volume in Asian populations [28]. Although the World Health Organization [29] used ≥25 kg/m² to define overweight, in South Asian males, a cutoff of 22.6 kg/m² has been proposed to define obesity since these subjects had a fat percentage equivalent to that of a White person with 30 kg/m² [30]. The American Diabetes Association now recommends a cut point of 23 kg/m² (rather than 25 kg/m²) for screening Asian patients for T2D [31]. In the present analysis, although Asian subjects with a BMI <25 kg/m² had a numerically greater reduction in HbA1c than those with a high BMI, further exploratory analyses suggested that the HbA1c-lowering efficacy of linagliptin was largely unaffected by baseline BMI. Indeed, the relationship between BMI and response to antidiabetes drugs such as DPP-4 inhibitors remains inconclusive with some reports showing an association [22, 23, 32] while others have not [33].

In this Asian multiethnic pooled analysis, Southeast Asian patients appeared to have greater reductions in HbA1c than other ethnic subgroups, but statistical analyses did not reveal interaction between ethnicity and treatment effect. On the other hand, other researchers have reported interethnic differences among Asians in the prevalence of T2D, distributions of risk factors (e.g., BMI, waist circumference), and beta-cell function [34, 35], as well as differences in HbA1c responses to treatment [36–38]. While more studies are needed to explore these subethnicity differences, our results and others showed comparable efficacy and safety of linagliptin in Japanese, Asian (non-Japanese), and White patients with T2D [39].

In our analysis, the efficacy of linagliptin in lowering iPPG may be particularly relevant to Asians with high carbohydrate intake and therefore high and fluctuating postprandial blood glucose excursion [16, 40, 41]. Hyperglycemia and glycemic variability might impair beta-cell function. Thus, it is plausible that lowering iPPG levels with linagliptin may slow the decline in beta-cell function [3, 42]. Indeed, previous reports have indicated improvements in beta-cell function with linagliptin treatment [18].
In common with all pooled analyses, the present study is limited by the inclusion of data from different clinical studies. However, this analysis was based on individual patient data from a large clinical development program in which the methodological approach was similar across all trials. Despite the relatively large sample size, volunteer effects and ethnic diversity mean that the results may not be fully generalizable to other Asian populations. Without inclusion of White patients, the relative efficacy between non-Asian and Asian populations has not been investigated, although in most of the primary studies, ethnicity was often adjusted in the final analysis. This latest pooled analysis provides additional data on the safety and efficacy of linagliptin in Asian populations.

CONCLUSION

In this global epidemic of T2D, Asian populations are disproportionately affected. Given the importance of beta-cell insufficiency and renal dysfunction in these Asian patients, as well as their high carbohydrate intake with associated high glucose excursions, linagliptin has a particular place in therapy for these high-risk subjects, irrespective of age, BMI, renal function, or subethnicity.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all trial participants.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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