Efficacy and safety of premixed insulin analogs in Asian patients with type 2 diabetes: A systematic review

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ABSTRACT

Aims/Introduction: The primary aim of this systematic review was to provide an overview of the efficacy and safety of premixed insulin analogs in Asians, specifically East Asians, with type 2 diabetes.

Material and Methods: The MEDLINE, Embase, Cochrane Library and ClinicalTrials.gov databases were searched from 1 January 1995 to 26 November 2015. Randomized controlled trials involving East Asians with type 2 diabetes treated with any premixed insulin analog were included. Major comparator treatments were basal insulin and basal–bolus insulin. Comparisons were also made between East Asian and Caucasian patients. The primary efficacy outcome was glycated hemoglobin change from baseline to end-point. The primary safety outcome was the incidence of hypoglycemia.

Results: A total of 21 studies were included; most (n = 14) were carried out in China or Japan. The duration of treatment ranged from 12 to 48 weeks. The glycated hemoglobin mean/least squares mean change from baseline to end-point after treatment with premixed insulin analogs ranged from −0.12 to −4.2% (improvement was generally more pronounced with insulin initiation vs intensification). The incidence of hypoglycemia ranged from 8.3 to 72.0% in most studies, with the variability reflecting the definition of hypoglycemia used. Efficacy and safety outcomes for premixed insulin analogs were generally similar to those for basal or basal–bolus insulin. Limited evidence suggests that dosing, efficacy and safety profiles might differ slightly between East Asian and Caucasians receiving premixed insulin analogs.

Conclusions: These results support the current use of premixed insulin analogs for managing East Asian patients with type 2 diabetes.

INTRODUCTION

The number of people with diabetes worldwide is increasing, and is estimated to reach 642 million by 20401. This increase in prevalence will be particularly pronounced in Asia, which is expected to account for more than 60% of the world’s diabetic population within the coming decades2. Clearly, research and dissemination of research findings, and examining the efficacy and safety of diabetes treatments is critical for optimizing treatment strategies required to address the worsening diabetes pandemic. One important factor that should be considered in such research is race/ethnicity, which can affect the characteristics of patients with diabetes and, possibly, their response to treatment. For instance, differences in genetic susceptibility, phenotype and underlying pathophysiology, age of onset, and body mass index (BMI) have been reported/suggested between Asians and Caucasians with diabetes3,4. Furthermore, there are differences in glycemic indices and glycemic load related to diet, whereby postprandial hyperglycemia plays a more prominent role in modulating glycated hemoglobin (HbA1c) in Asians than Caucasians5,6. Given these differences and the projected increase in the prevalence of diabetes in the region, studies assessing the efficacy and safety of diabetes treatments in Asians are of obvious importance.
Most patients with type 2 diabetes will require treatment with insulin and, with disease progression, intensification of insulin therapy. Basal insulin or premixed insulin analogs are typically prescribed for initiation (depending on the country), whereas basal–bolus insulin or premixed insulin analogs are typically prescribed for intensification. Of these treatment options, premixed insulin analogs are widely used in some East Asian countries. Indeed, approximately two-thirds of Chinese patients taking oral antihyperglycemic drugs and insulin use insulin in the form of premixed insulin10, and approximately one-third of Japanese patients initiate insulin therapy with premixed insulin11. Despite the wide (and recommended12,13) use of premixed insulins, there is relatively little information in the literature on their efficacy and safety in Asian populations. Furthermore, although the findings from a number of randomized controlled trials have been published, to date, there have been no systematic collation/meta-analyses of findings from randomized controlled trials.

The primary aim of the present systematic review was to review the relative effectiveness and safety of premixed insulins in Asians, specifically East Asians, with type 2 diabetes as determined in randomized controlled trials. Secondary aims were to compare the efficacy and safety of premixed insulin analogs with basal or basal–bolus insulin, and between East Asians and Caucasians.

MATERIALS AND METHODS

Eligibility criteria

Study design and participants

Published evidence from randomized controlled trials involving patients with type 2 diabetes and a minimum of 12 weeks of treatment (and meta-analyses of such trials) was included. Evidence from other study designs was excluded. Narrative/systematic reviews were also excluded; however, reference lists from such articles were screened to identify potentially eligible studies not detected in the literature search.

Interventions

Studies involving treatment with any premixed insulin analog were included. For studies comparing premixed insulin analogs with other insulin treatments, other treatments were restricted to any basal insulin, basal–bolus insulin or premixed human insulin.

Outcome measures

Outcome measures were collected as reported. Efficacy outcomes were HbA1c, fasting blood glucose/fasting plasma glucose (FPG), self-monitoring of blood/plasma glucose (SMBG/SMPG) and insulin dose. Safety outcomes were hypoglycemia and bodyweight/BMI.

Setting

Studies carried out in East Asian countries/regions (China, Hong Kong, Japan, Korea, Macao, Mongolia, Taiwan) were included, as were multinational studies where separate results for East Asians and Caucasians were available. Studies reporting outcomes from mixed populations (East Asian and non-East Asian) or subgroup analyses of patients of East Asian descent/origin living in non-East Asian countries were excluded.

Information sources

The following databases were searched (1 January 1995 to 26 November 2015): MEDLINE and Embase via Ovid, The Cochrane Library, and ClinicalTrials.gov.

Search strategy

The databases were searched using search terms (Medical Subject Heading [MeSH], EMTREE and/or free text) from three categories: (i) premixed insulin analogs (30% soluble insulin aspart, 70% protamine-crystallized insulin aspart [BIAsp]; Humalog; insulin aspart; insulin lispro; insulin mixture*; lispro; Novolog; Novomix; Novorapid; premixed insulin analog*; premixed insulin [* indicates wild card truncation]); (ii) East Asia (China; East Asia*; Hong Kong; Japan; Korea; Macao; Mongolia; Taiwan); and (iii) type 2 diabetes (diabetes mellitus, type 2; non-insulin dependent diabetes mellitus; T2D*; type 2 diabetes; type 2 diabetes mellitus).

Where possible, search terms and strategies were individualized to each database. Terms were combined using ‘OR’ and ‘AND’. As an example, MEDLINE was searched using the following strategy: (insulin aspart [MeSH] OR insulin lispro [MeSH] OR BIAsp OR Humalog OR insulin aspart OR insulin lispro OR insulin mixture* OR lispro OR Novolog OR Novomix OR Novorapid OR premixed insulin analog* OR premixed insulin) AND (China [MeSH] OR Hong Kong [MeSH] OR Japan [MeSH] OR Korea [MeSH] OR Macao [MeSH] OR Mongolia [MeSH] OR Taiwan [MeSH] OR China OR East Asia* OR Hong Kong OR Japan OR Korea OR Macao OR Mongolia OR Taiwan) AND (diabetes mellitus, type 2 [MeSH] OR T2D* OR type 2 diabetes OR type 2 diabetes mellitus).

There were no restrictions on language.

Study records

Searches were collated using a bibliography manager, and duplicates were removed. One reviewer screened the title and abstract of each publication identified, and applied the eligibility criteria to identify publications that required further review. All authors were consulted if inclusion was uncertain, and reviewed and approved all articles selected for inclusion. One person extracted all data from the included publications into standardized data tables.

Study characteristics

Study characteristics collected included publication year, study design, intervention and type of control/comparator, treatment regimen, and source of financial support.
Outcomes
The primary efficacy outcome was HbA1c change from baseline to end-point. Secondary efficacy outcomes were the proportion of patients attaining HbA1c targets, fasting blood glucose/FPG and SMBG/SMPG change from baseline to end-point, and total daily insulin dose at study end-point.

The primary safety outcome was the incidence of hypoglycemia. The secondary outcome was the rate of hypoglycemia and bodyweight/BMI change from baseline.

Risk of bias
Each study was rated as having a low, high or unclear risk of bias regarding sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

RESULTS
Study selection
A total of 536 studies were identified in the search of published literature (Figure 1). Of these, 165 were duplicates and 356 were excluded. Three additional studies were identified (including two that had been submitted, but not published at the time of the literature search); hence, 18 studies from the literature were included in the review. Three eligible studies were identified in the search of ClinicalTrials.gov and included.

Study characteristics
Most studies were carried out in China or Japan; there were four multicountry studies (Table 1). The studies were generally similar in design, but of variable duration (Table 1). All had parallel treatment arms, except for one study that had a cross-over design. The duration of treatment ranged from 12 to 48 weeks; however, approximately half of the studies had a duration of 24–28 weeks of treatment.

Most studies included patients with a minimum HbA1c of ≥7.0 or ≥7.5% (Table 1). One study included patients on the basis of FPG and postprandial plasma glucose concentrations (≥7 and ≥11.1 mmol/L, respectively).

Most studies were of initiation (14 studies), rather than intensification (six studies), of insulin therapy (Table 1). In one study, patients were switched from premixed human insulin to a premixed insulin analog.

Premixed insulin analogs used in the studies included the low mixtures 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart (BIAsp30, 12 studies); 25% insulin lispro, 75% insulin lispro protamine suspension (LM25, six studies); the mid mixture 50% insulin lispro, 50% insulin lispro protamine suspension (LM50, seven studies); and the high mixture 70% soluble insulin aspart, 30% protamine-crystallized insulin aspart (BIAsp70, one study).

Control/comparator interventions included basal–bolus insulin (seven studies), basal insulin (two studies) and premixed human insulin (two studies). Different premixed insulin analogs or premixed insulin analog treatment regimens were compared in nine studies.

Treatment regimens were variable between studies, with doses titrated to achieve blood glucose, plasma glucose and/or HbA1c targets (Table 1). Except for sulfonylureas, prior oral

Figure 1 | Literature search flow diagram.
# Table 1 | Summary of study characteristics

| Study author and year (or CT.gov identifier) | Countries/regions | Study design | Duration | Key eligibility criteria | Previous treatment | Study treatment (no. patients) | Treatment regimen | Sponsor/funding |
|-------------------------------------------|-------------------|--------------|----------|--------------------------|--------------------|-----------------------------|-----------------|----------------|
| **Initiation of insulin therapy**         |                   |              |          |                          |                    |                             |                 |                |
| Masuda (2008)17                           | Japan             | R, OL        | 12 weeks | HbA1c ≥7.0%, insulin naïve | OADs               | LM50 (n = 14)                | LM50 twice daily | NR             |
|                                           |                   |              |          |                          |                    | NPH insulin + insulin lispro (n = 14) | NPH insulin at bedtime + prandial insulin lispro |                |
|                                           |                   |              |          |                          |                    | First 10 days                | All doses titrated to achieve FPG <130 mg/dL and 2 h postprandial PG <180 mg/dL, >10 days |                |
|                                           |                   |              |          |                          |                    |                              | All doses titrated to achieve HbA1c <7.0% with minimal hypoglycemia |                |
| Ji (2016)15                               | China, Korea      | R, OL        | 48 weeks | HbA1c ≥7.0 and ≤11.0%, insulin naïve | OADs               | LM25                         | LM25 once daily before dinner, progressing to thrice daily (doses titrated to achieve FBG/pre-evening meal BG 4.5–6.0 mmol/L) | Eli Lilly       |
|                                           |                   |              |          |                          |                    | East Asian (n = 45)          | Insulin glargine once daily at bedtime (dose titrated to achieve FBG 4.5–6.0 mmol/L) + insulin lispro up to thrice daily (doses titrated to achieve premeal/bedtime BG 4.5–6.0 mmol/L) |                |
|                                           |                   |              |          |                          |                    | Caucasian (n = 69)           |                              |                |
|                                           |                   |              |          |                          |                    | Insulin glargine + insulin lispro |                              |                |
|                                           |                   |              |          |                          |                    | East Asian (n = 44)          |                              |                |
|                                           |                   |              |          |                          |                    | Caucasian (n = 61)           |                              |                |
|                                           |                   |              |          |                          |                    | Continuation of OADs (all patients) |                              |                |
| Zhang (2010)18                            | China             | R, OL, cross-over | 12 weeks on each arm (24 weeks total) | FPG ≥7 mmol/L, PPG ≥11.1 mmol/L | OADs | LM50 (n = 30) | Induction (10 days) | NR             |
|                                           |                   |              |          |                          |                    | Premixed human insulin 70/30 (n = 30) | All patients: Premixed human insulin 70/30 (starting dose: 0.5–0.6 IU/kg) |                |
|                                           |                   |              |          |                          |                    | MET (obese patients only)    | Week 1–12 and Week 13–24 LM50 or premixed human insulin 70/30 (doses titrated to achieve FPG 5–8 mmol/L and PPG 6–10 mmol/L) |                |
| Miyashita (2008)19                        | Japan             | R, OL        | 6 months | HbA1c ≥8.0                | OADs               | BIAsp30 (n = 21)              | BIAsp30 before breakfast and dinner | NR             |
|                                           |                   |              |          |                          |                    | NPH insulin + insulin aspart (n = 21) | NPH insulin + insulin aspart at night on an on-demand basis |                |
|                                           |                   |              |          |                          |                    | Continuation of MET and TZDs (all patients) | First 7 days: All doses titrated every 2–3 days to achieve fasting glucose <130 mg/dL and 2 h postprandial glucose <180 mg/dL, >7 days: All doses titrated monthly to achieve HbA1c <6.5% |                |
Table 1 (Continued)

| First author and year (or CT.gov identifier) Countries/regions | Study design Duration | Key eligibility criteria | Previous treatment | Study treatment (no. patients) | Treatment regimen | Sponsor/ funding |
|---------------------------------------------------------------|-----------------------|-------------------------|--------------------|----------------------------------|-------------------|-----------------|
| Hirao (2009) Japan                                           | R, OL 6 months        | HbA1c ≥8.0, insulin naïve | OADs               | BIAsp30 (n = 80) Insulin aspart ± NPH insulin (n = 80)<sup>1</sup> | BIAsp30 twice daily | Japan Diabetes Foundation |
| Lee (2011)<sup>31</sup> Korea                               | R, OL 16 weeks        | Previous SU treatment, HbA1c >7.5%, insulin naïve | SU                 | BIAsp30 (n = 59) Insulin detemir (n = 61) Continuation non-SU OADs (all patients) | After 3 weeks, patients with glycated albumin ≤20% or who had major or frequent hypoglycemia switched to twice-daily BIAsp30 before breakfast and dinner (doses titrated to achieve fasting glucose <6.1 mmol/L without significant hypoglycemia) | Yonsei University College of Medicine |
| Yang (2013)<sup>21</sup> China, Japan                        | R, OL 24 weeks        | HbA1c ≥7.0 and ≤10.0%, FPG ≥6.1 mmol/L, insulin naïve | OADs               | BIAsp30 (n = 261) Insulin glargine (n = 260) GLIM + MET (all patients) | Once daily (doses titrated to achieve prebreakfast FPG 5.0–6.1 mmol/L GLIM 4 mg/day, MET 1,500 or 2,500 mg/day Before breakfast & dinner (doses titrated to achieve FBG ≥4.4 and ≤6.1 mmol/L) | Novo Nordisk |
| Zafar (2015)<sup>22</sup> China                              | R, OL 12 weeks        | HbA1c ≥7.5%, FBG ≥7.8 mmol/L, insulin naïve | OADs               | LM50 (n = 73) LM25 (n = 73) | Before breakfast & dinner (doses titrated to achieve FBG >3.9 and ≤6.1 mmol/L) | Ministry of Education, People’s Republic of China |
| Su (2015)<sup>23</sup> China NCT01476273 China               | R, OL 26 weeks        | HbA1c ≥7.0 and ≤11.0% | OADs               | LM25 (n = 80) LM50 (n = 76) LM25 (n = 138)<sup>4</sup> | Before breakfast & dinner (doses titrated to achieve FBG >3.9 and ≤6.1 mmol/L) Doses titrated following a forced schedule per BG before breakfast and dinner Before dinner (dose titrated to achieve HbA1c <7.4%) + injections before breakfast and before lunch after 16 and 32 weeks, respectively, if HbA1c <7.4% | Eli Lilly Sun Yat-sen University |
| Domeki (2014)<sup>34</sup> Japan                             | R, OL 48 weeks        | HbA1c ≥8.4%, insulin naïve | OADs               | LM50 (n = 36) BIAsp30 (n = 36) Continuation of OADs (all patients) | Before dinner (dose titrated to achieve HbA1c <7.4%) + injections before breakfast and before lunch after 16 and 32 weeks, respectively, if HbA1c <7.4% | NR |
| Yang (2008)<sup>25</sup> China                               | R, OL 24 weeks        | HbA1c ≥7.5% and FBG ≥7.8 mmol/L, insulin naïve | OADs               | BIAsp30 × 2 (n = 160) BIAsp30 × 3 (n = 161) Continuation of OADs (all patients) | BIAsp30 before breakfast & dinner (50:50%) BIAsp30 before breakfast, lunch & dinner (25:25:50%) All doses titrated to achieve premeal BG 4.4–6.1 mmol/L | Novo Nordisk |

<sup>1</sup> Previously treated with sulfonylurea (SU) or metformin (MET).<sup>2</sup> Previously treated with a thiazolidinedione (TZD).<sup>3</sup> Previously treated with a glucagon-like peptide 1 receptor agonist (GLP-1 RA).<sup>4</sup> Previously treated with a dipeptidyl peptidase 4 inhibitor (DPP-4i).<sup>5</sup> Previously treated with a sodium-glucose cotransporter 2 inhibitor (SGLT2i).
| First author and year (or CT.gov identifier) | Countries/regions | Study design | Duration | Key eligibility criteria | Previous treatment | Study treatment (no. patients) | Treatment regimen | Sponsor/funding |
|---------------------------------------------|-------------------|--------------|----------|-------------------------|---------------------|------------------------------|------------------|-----------------|
| Ebato (2009)26                              | Japan             | R, OL        | 48 weeks | HbA1c >8.0%, insulin naïve | OADs                | BIASp30 + GLIM (n = 14)        | Week 1–24        | Novo Nordisk    |
|                                             |                   |              |          |                         |                     | BIASp30 (n = 12)              |                  |                 |
|                                             |                   |              |          |                         |                     | Continuation of OADs (all     |                  |                 |
|                                             |                   |              |          |                         |                     | patients)                    |                  |                 |
|                                             |                   |              |          |                         |                     | GLIM 3 mg/day                |                  |                 |
|                                             |                   |              |          |                         |                     | Week 25–48                   |                  |                 |
|                                             |                   |              |          |                         |                     | BIASp30 before breakfast & dinner (doses titrated to achieve before breakfast & before dinner BG 101–150 mg/dL ± GLIM 3 mg/day) | |                 |
|                                             |                   |              |          |                         |                     | Before breakfast & dinner (doses titrated to achieve preprandial BG ≥4.4 and ≤6.1 mmol/L) | |                 |
| Jung (2014)27                               | Korea             | R, OL        | 24 weeks | HbA1c ≥7.5%, insulin naïve | OADs                | BIASp30 (moming : evening ratio) | | NR              |
|                                             |                   |              |          |                         |                     | 50:50% (n = 33)              |                  |                 |
|                                             |                   |              |          |                         |                     | 55:45% (n = 34)              |                  |                 |
|                                             |                   |              |          |                         |                     | 60:40% (n = 33)              |                  |                 |
|                                             |                   |              |          |                         |                     | Continuation of OADs, except SU (all patients) | |                 |
| Jeong (2016)16                              | China, Korea      | R, OL, non- inferiority | 24 weeks | HbA1c ≥7.5 and ≤10.5%, FPG ≤6.7 mmol/L | Insulin glargine, OADs | LM25 (n = 40) | Eli Lilly       |
|                                             |                   |              |          |                         |                     | East Asian (n = 40)          |                  |                 |
|                                             |                   |              |          |                         |                     | Caucasian (n = 136)          |                  |                 |
|                                             |                   |              |          |                         |                     | Insulin glargine + insulin lispro (n = 202) | |                 |
|                                             |                   |              |          |                         |                     | Continuation of OADs (all patients) | |                 |
|                                             |                   |              |          |                         |                     | East Asian (n = 40)          |                  |                 |
|                                             |                   |              |          |                         |                     | Caucasian (n = 143)          |                  |                 |
|                                             |                   |              |          |                         |                     | MET and/or PIO (all patients) |                  |                 |
Table 1 (Continued)

| First author and year (or CT.gov identifier) | Study design | Countries/regions | Key eligibility criteria | Previous treatment | Study treatment (no. patients) | Treatment regimen | Sponsor/ funding |
|--------------------------------------------|--------------|-------------------|--------------------------|--------------------|-------------------------------|------------------|-----------------|
| Jin (2015) Korea                            | R, OL, non-inferiority | 24 weeks         | HbA1c ≥7.0 and ≤10.0%, and FPG <130 mg/dL on insulin glargine for ≥12 weeks | Insulin glargine + OADs | BIAsp30 (n = 83) Insulin glargine + insulin glulisine (n = 78) Continuation of OADs (all patients) | BIAsp before breakfast & dinner (doses titrated to achieve FPG 70–100 mg/dL) Insulin glargin in evening (dose titrated to achieve FPG 70–100 mg/dL) + insulin glulisine before main meal (dose titrated to achieve 2 h postprandial BG ≤140 mg/dL), with second injection added before second main meal for patients with HbA1c >7% after 12 weeks | Sanofi Korea |
| Kadowaki (2010) Japan                       | R, OL, non-inferiority | 28 weeks         | HbA1c between 7.5 and 100% | Intermediate-acting, long-acting human, and/or premixed human insulin | BIAsp70 (n = 145) BIAsp30 (n = 144) BIASp before each main meal BIASp30 before breakfast and dinner** All doses titrated to achieve FPG <130 mg/dL and 2 h postprandial PG <180 mg/dL | Novo Nordisk |
| NCT01278160 China                          | R, OL         | 16 weeks         | HbA1c ≥7%, completed 24 weeks treatment with BIASp30 or insulin glargine + MET and GLIM in preceding trial | BIASp30 or insulin glargine, OADs | BIAsp30 67.3% (n = 89) BIAsp30 50.50% (n = 90) MET (all patients) | BIAsp30 before breakfast & dinner (67:33 or 50:50%) MET 500 mg/day | Novo Nordisk |
| Switch from premixed human insulin         | R, OL         | 20 weeks         | HbA1c ≥7 and ≤9.5%, treatment with premixed/self-mixed human insulin + MET ± α-glucosidase inhibitor, total daily insulin dose <1.4 U/kg | Premixed human insulin + OADs | BIAsp30 patient-driven titration (n = 172) BIAsp30 investigator-driven titration (n = 172) Continuation of OADs (all patients) | Twice daily Doses titrated | Novo Nordisk |

*62.5% of patients in this group received neutral protamine Hagedorn (NPH) insulin; †Information on NPH insulin dosing not provided; ‡Comparator groups in this study included patients treated with exenatide or pioglitazone and were therefore not eligible for inclusion in this review; ††Patients with glycated hemoglobin (HbA1c) <7.0% at week 24 were excluded; †‡ Patients who failed to achieve the target prebreakfast plasma glucose (PG) level of <130 mg/dL at 16 weeks could have their predinner formulation switched to 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart (BIAsp30). BG, blood glucose; BIAsp30, 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart; BIAsp70, 70% soluble insulin aspart, 30% protamine-crystallized insulin aspart; CT.gov, ClinicalTrialsgov; FBG, fasting blood glucose; FPG, fasting plasma glucose; GLIM, glimepiride; LM25, 25% insulin lispro, 75% insulin lispro protamine suspension; LM50, 50% insulin lispro, 50% insulin lispro protamine suspension; MET, metformin; NR, not reported; OADs, oral antihyperglycemic drugs; OL, open-label; PIO, pioglitazone; PPG, postprandial glucose; R, randomized; SU, sulfonylurea; TGD, thiazolidinediones.
antidiabetic drugs were generally continued during study treatment.

Risk of bias

The studies were generally considered to have a high risk of potential bias because of the open-label design, but a low risk of potential bias because of incomplete outcome data, selective outcome reporting and other sources of bias (Table 2). More than half of the studies provided insufficient information to make adequate assessment of potential bias related to sequence generation, allocation concealment and blinding of outcome assessors.

Efficacy outcomes

In all studies, HbA1c levels decreased from baseline to end-point after treatment with premixed insulin analogs (where reported, the difference between baseline and end-point was generally statistically significant; Table 3). The HbA1c mean/least squares mean changes ranged from −0.12 to −4.2% among all studies, −0.16 to −4.2% in studies where patients received initiation of insulin therapy and −0.12 to −1.32% in studies where patients received intensification of insulin therapy.

A total of 15 studies\textsuperscript{15,16,20,21,23–27,29–32,34,35} reported data on the proportion of patients attaining HbA1c targets after treatment with premixed insulin analogs (Table 3). The proportion of patients attaining the HbA1c target of ≤7% ranged from 8.3 to 72.4% among all studies, 8.3 to 72.4% in studies where patients received initiation of insulin therapy and 12.4 to 33.3% in studies where patients received intensification of insulin therapy. The proportion of patients attaining the HbA1c target of ≤6.5% ranged from 2.2 to 59.1% among all studies, 14.9 to 59.1% in studies where patients received initiation of insulin therapy and 2.2 to 17.9% in studies where patients received intensification of insulin therapy.

Of the 10 studies reporting data, fasting blood glucose/FPG concentrations decreased from baseline to end-point in seven studies\textsuperscript{17,18,22–24,27,34}, and increased from baseline to end-point in three studies\textsuperscript{16,28,29} after treatment with premixed insulin analogs (Table 3; note: few studies statistically compared baseline and end-point data). Fasting blood glucose/FPG concentrations were decreased from baseline in six studies\textsuperscript{17,18,22–24,27} where patients received initiation of insulin therapy, increased from baseline in three studies\textsuperscript{16,28,29} where patients received intensification of insulin therapy, and decreased from baseline

| First author and year (or CT.gov identifier) | Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessors | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|---------------------------------------------|---------------------|-----------------------|--------------------------------------|-----------------------------|------------------------|---------------------------|-----------------------|
| Masuda (2008)\textsuperscript{17} | × | + | × | ? | + | + | + |
| Ji (2016)\textsuperscript{15} | + | + | × | ? | ? | ? | ? |
| Zhang (2010)\textsuperscript{18} | × | ? | × | ? | ? | ? | ? |
| Miyashita (2008)\textsuperscript{19} | + | ? | ? | ? | ? | ? | ? |
| Hira (2009)\textsuperscript{20} | × | ? | × | ? | ? | ? | ? |
| Lee (2011)\textsuperscript{31} | × | ? | × | ? | ? | ? | ? |
| Yang (2013)\textsuperscript{21} | × | ? | × | ? | ? | ? | ? |
| Zafar (2015)\textsuperscript{22} | × | ? | × | ? | ? | ? | ? |
| Su (2015)\textsuperscript{23} | + | + | × | ? | ? | ? | ? |
| NCT01147627\textsuperscript{33} | × | ? | × | ? | ? | ? | ? |
| Dorni (2014)\textsuperscript{24} | × | ? | × | ? | ? | ? | ? |
| Yang (2008)\textsuperscript{25} | + | + | × | ? | ? | ? | ? |
| Ebato (2009)\textsuperscript{26} | × | ? | × | ? | ? | ? | ? |
| Jung (2014)\textsuperscript{27} | + | + | × | ? | ? | ? | ? |
| Yamada (2007)\textsuperscript{28} | + | + | × | ? | ? | ? | ? |
| Jia (2015)\textsuperscript{29} | + | + | × | ? | ? | ? | ? |
| Jeong (2016)\textsuperscript{16} | + | ? | × | ? | ? | ? | ? |
| Jin (2015)\textsuperscript{29} | + | + | × | ? | ? | ? | ? |
| Kadowski (2010)\textsuperscript{30} | × | ? | × | ? | ? | ? | ? |
| NCT01618214\textsuperscript{34} | × | ? | × | ? | ? | ? | ? |
| NCT01278160\textsuperscript{35} | × | ? | × | ? | ? | ? | ? |

\textcolor{red}{\textsuperscript{a}} Low risk; \textcolor{blue}{?} unclear risk; \textcolor{green}{=} high risk.
Table 3 | Summary of study outcomes

| First author and year | HbA1c change | % Patients achieving HbA1c targets | FBG/FPG change | SMBG/SMPG change | Total daily insulin dose at end-point | Definition of hypoglycemia Incidence | Bodyweight/BMI change |
|-----------------------|--------------|-----------------------------------|----------------|------------------|--------------------------------------|--------------------------------------|----------------------|
| **Initiation of insulin therapy** | | | | | | | |
| Masuda (2008) | −4.2 vs −4.4% (P = NR) | NR | FPG | NR | 0.40 vs 0.45 IU/kg (P = NS) | Not defined (NR) | BMI | −0.3 vs +0.2 kg/m² (P = NS for rate/patient) |
| LM50 vs NPH insulin + insulin lispro | | | −151 vs −171 mg/dL (P = NR) | | | | | Bodyweight | East Asian: +2.95 vs +2.81 kg Caucasian: +3.00 vs +3.43 kg (P = NR for East Asian vs Caucasian) |
| Ji (2016) | LS mean East Asian: −2.03 vs −1.76% Caucasian: −2.07 vs −2.05% (P = NS for East Asian vs Caucasian) | HbA1c <7% East Asian: 37.5 vs 36.1% Caucasian: 51.7 vs 48.1% (P = NS for East Asian vs Caucasian) | NR | NR | East Asian: 0.42 vs 0.46 IU/kg Caucasian: 0.57 vs 0.50 IU/kg (P = NS for East Asian vs Caucasian) | Doc/undoc sympt, asympt Overall East Asian: 69.8 vs 77.3% Caucasian: 94.1 vs 91.8% Nocturnal East Asian: 41.9 vs 52.3% Caucasian: 83.8 vs 78.7% Severe East Asian: 7.0 vs 0% Caucasian: 2.9 vs 4.9% (P = NS for % change) | Bodyweight | East Asian: +2.95 vs +2.81 kg Caucasian: +3.00 vs +3.43 kg (P = NS for East Asian vs Caucasian) |
| Zhang (2010) | Week 12 −1.72 vs −1.56% Week 24 −0.16 vs +0.02% | NR | FPG Week 12 −0.1 vs −0.3 mmol/L Week 24 +0.1 vs −0.2 mmol/L | NR | Week 12 35.8 vs 40.6 IU Week 24 28.8 vs 34.1 IU | Not defined (NR) (episodes/patient/study period: week 12, 6.0 vs 99 events; week 24, 35 vs 68 events) | Bodyweight | East Asian: +2.95 vs +2.81 kg Caucasian: +3.00 vs +3.43 kg (P = NS for East Asian vs Caucasian) |
| Miyashita (2008) | −1.9 vs 2.0% (P = 0.32 for % change) | NR | NR | 7-point SMBG No significant differences between groups at any time-point | 0.39 vs 0.44 IU/kg (P = NR) | Bodyweight | East Asian: +2.95 vs +2.81 kg Caucasian: +3.00 vs +3.43 kg (P = NS for East Asian vs Caucasian) |
| First author and year (or CT.gov identifier) | Treatment Groups | HbA1c change† | % Patients achieving HbA1c targets | FBG/FPG change† | SMBG/SMPG change† | Total daily insulin dose at end-point | Definition of hypoglycemia Incidence | Bodyweight/BMI change† |
|--------------------------------------------|------------------|----------------|-----------------------------------|-----------------|-------------------|-------------------------------------|----------------------------------|------------------|
| Hirao (2009)20 | BIASp30 vs insulin aspart ± NPH insulin | −2.6 vs −2.6% (P = NS) | HbA1c <7%: 32.1 vs 32.8% (P = NS) | HbA1c <6.5%: 17.9 vs 16.4% (P = NS) | NR | NR | NR | Not defined | BMI |
| Lee (2011)31 | BIASp30 once daily vs BIASp30 twice daily | −1.25 vs −0.70 vs −1.75% (P = 0.015) | HbA1c ≤7%: 43 vs 36 vs 41% (P = 0.928) | NR | NR | NR | NR | NR |
| Yang (2013)21 | BIASp30 vs insulin glargine | −0.78 vs −0.65% Non-inferiority demonstrated | HbA1c <7%: 29.1 vs 30.0% (P = 0.858) | HbA1c ≤6.5%: 14.9 vs 14.2% (P = 0.801) | NR | 9-point SMPG | 17.8 vs 18.2 IU (P = NR) | Doc/undoc sympt, asympt | Bodyweight |
| Zafar (2015)22 | LM50 vs LM25 | −4.2 vs −3.6% (P < 0.05) | NR | FBG | −2.6 vs −1.1 mmol/L (P < 0.05) | NR | 0.84 vs 0.87 IU/kg (P = 0.17) | Doc sympt | Bodyweight |
| Su (2015)23 | LM25 vs LM50 | LS mean −1.55 vs −2.03% (P < 0.001) | HbA1c <7%: 45.0 vs 72.4% (P = 0.001) | HbA1c ≤6.5%: 22.5 vs 59.1% (P < 0.001) | FBG LS mean | −2.50 vs −2.12 mmol/L (P = 0.180) | 7-point SMBG | 38.6 vs 36.2 IU (P = NS) | Doc/undoc sympt, asympt | Bodyweight |
| NCT0114762933 | LM25 | −1.74% | NR | NR | NR | NR | NR | LS mean | Bodyweight |

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Table 3 (Continued)

| First author and year (or CT.gov identifier) | Treatment Groups | HbA1c change † | % Patients achieving HbA1c targets | FBG/FPG change † | SMBG/SMPG change † | Total daily insulin dose at end-point | Definition of hypoglycemia Incidence | Bodyweight/ BMI change † |
|---------------------------------------------|------------------|----------------|-----------------------------------|------------------|------------------|--------------------------------------|--------------------------------------|-------------------------|
| Domeki (2014)24                             | LM50 vs BIASp30  | −1.9 vs −1.7% (P = NS at baseline & end-point) | HbA1c < 7.4%: 72.2 vs 66.7% (P = NS) | FPG −40 vs −33 mol/L (P = NS at baseline & end-point) | NR | NR | Not defined | BMI +2.7 vs +6.1 kg/m² (P = NS at baseline & end-point) |
| Yang (2008)25                               | BIASp30 × 2 vs ×3 | −2.48 vs −2.81% (P < 0.01) ×3 superior to ×2 | HbA1c < 7%: 51.3 vs 65.8% (P < 0.01) HbA1c ≤ 5.9%: 34.4 vs 46.6% (P < 0.05) | NR | NR | 0.82 vs 0.86 IU/kg (P = 0.19) Doc sympt, asympt Minor: 23 vs 19% (P = NS) Major: 0.63 vs 1.9% (P = NS) | Bodyweight +3.87 vs +4.09 kg (P = NS) |
| Ebato (2009)26                              | BIASp30 + GLIM vs BIASp30 | −2.33 vs −1.18% (P = NR) | HbA1c < 7%: 50.0 vs 83.0% (P = NR) | NR | NR | 0.21 vs 0.36 IU/kg (P < 0.05) Doc sympt, asympt Minor: 0 vs 0% Major: 0 vs 0% | Bodyweight No change (data NR) |
| Jung (2014)27                               | BIASp30 50:50 vs 55:45 vs 60:40 | LS mean −1.27 vs −1.05 vs −1.03 (P = 0.623) | HbA1c < 7%: 79.6 vs 25.0 vs 25.9% (P = NS) | FPG −1.1 vs −1.6 vs −1.0 mmol/L (P = NS for LS mean changes [values NR]) | NR | NR | 0.45 vs 0.46 vs 0.54 IU/kg (P = 0.142) Doc sympt, asympt Minor: 0 vs 0% Major: 0 vs 0% | Bodyweight +1.72 vs +1.98 kg (P = NS) |
| Jia (2015)32                                | LM50 + LM25 vs insulin glargine + insulin lispro | LS mean −1.1 vs −1.1% Non-inferiority demonstrated | HbA1c ≤ 7%: 29.9 vs 34.2% (P = 0.392) HbA1c ≤ 5.9%: 9.1 vs 11.9% (P = NR) | NR | NR | 0.38 vs 0.37 IU/kg (P = NS) | Severe: 0 vs 0% BMI +0.3 vs −0.2 kg/m² (P = NS) |

**Intensification of insulin therapy**

| Yamada (2007)28                             | LM50 vs premixed human insulin | −0.35 vs −0.04% (P < 0.05) | NR | FBG +28.2 vs −5.4 mg/dL (P = NS) | NR | NR | 0.38 vs 0.37 IU/kg (P = NS) | Severe: 0 vs 0% BMI +0.3 vs −0.2 kg/m² (P = NS) |
| Jia (2015)32                                | LM50 + LM25 vs insulin glargine + insulin lispro | LS mean −1.1 vs −1.1% Non-inferiority demonstrated | HbA1c ≤ 7%: 29.9 vs 34.2% (P = 0.392) HbA1c ≤ 5.9%: 9.1 vs 11.9% (P = NR) | NR | NR | 7-point SMBG | 52.93 vs 53.99 IU (P = 0.106) Not defined | Bodyweight +0.8 kg vs +0.7 kg (P = NR) |

7-point SMBG

Midday 2 h postprandial, evening premeal, & 03:00 h significantly reduced (P < 0.05) for BIASp30 vs insulin glargine + insulin lispro; Morning premeal significantly reduced for insulin glargine + insulin lispro vs BIASp30 (P = 0.002)
| First author and year (or CT.gov identifier) | Treatment Groups | HbA1c change† | % Patients achieving HbA1c targets | FBG/FPG change† | SMBG/SMPG change† | Total daily insulin dose at end-point | Definition of hypoglycemia Incidence | Bodyweight/BMI change† |
|--------------------------------------------|------------------|--------------|-------------------------------|----------------|----------------|-------------------------------------|---------------------------------|---------------------|
| Jeong (2016)16                             | LM25 vs insulin glargine + insulin lispro | East Asian: −1.3 vs −0.9% (P < 0.001) | HbA1c <7% East Asian: 33.3 vs 22.9% (P = NS) | FBG East Asian: 0.40 vs 0.25 mmol/L (P = NS) | 7-point SMBG Mean change from baseline similar in both arms for both subpopulations | East Asian: 0.56 vs 0.59 IU/kg (P = NR) | Doc sympt Overall East Asian: 65.0 vs 82.1% (P = NR) Caucasian: 69.9 vs 64.1% (P = NR) | Bodyweight East Asian: +0.62 vs +0.51 kg (P = NR) Caucasian: 1.77 vs 0.67 kg (P = NR) |
| Jin (2015)29                               | BIAsp30 vs insulin glargine + insulin glulisine | −1.07 vs −0.91% (P = 0.358) Non-inferiority demonstrated | HbA1c <7%: 29.3 vs 33.3% (P = 0.773) HbA1c ≤6.5%: 14.6 vs 14.1% (P = 0.794) | FPG 24.44 vs 3.11 mg/dL (P < 0.001) | 7-point SMBG Before breakfast & 2 h after lunch significantly reduced (P < 0.05) for insulin glargine + insulin glulisine vs BIAsp30 | No between group difference (values NR) | Doc/undoc sympt, asympt Baseline–Week 12 Overall: 68.3 vs 88.5% (P = 0.002) Nocturnal: 23.2 vs 34.6% (P = 0.110) Severe: 0 vs 1.3% (P = 0.488) Week 12–24 Overall: 72.0 vs 69.2% (P = 0.230) Nocturnal: 30.5 vs 25.6% (P = 0.665) Severe: 1.2 vs 2.6% (P = 0.739) | Body weight +1.05 vs +1.22 kg (P = 0.537) |
Table 3  (Continued)

| First author and year | HbA1c change $^a$ | % Patients achieving HbA1c targets | FBG/FPG change $^b$ | SMBG/SMPG change $^b$ | Total daily insulin dose at end-point | Definition of hypoglycemia Incidence | Bodyweight/ BMI change $^c$ |
|-----------------------|------------------|-----------------------------------|-------------------|-----------------------|--------------------------------------|-------------------------------------|-----------------------------|
| Kadowaki (2010)$^{30}$ | $-1.32$ vs $-0.99\%$ Non-inferiority shown | HbA1c $<6.5\%$: 16.0 vs 11.9\% ($P = NR$) | NR | 7-point SMPG Mean PPG increment: 22.8 vs 47.5 mg/dL ($P = NR$) | 46.8 vs 38.1 IU/day ($P = NR$) | Doc/undoc sympt, asympt | Bodyweight $+1.94$ vs $+1.23$ kg ($P = 0.011$) |
| NCT01278160$^{35}$ | LS mean $-0.13$ vs $-0.12$ | HbA1c $<7\%$: 12.4 vs 14.4\% ($P = 0.731$) HbA1c $\leq 6.5\%$: 2.2 vs 78\% ($P = 0.126$) | NR | 9-point SMPG No significant differences between groups at any time-point | NR | Doc sympt, asympt | NR |
| NCT01618214$^{34}$ | $-1.32$ vs $-1.31\%$ Non-inferiority demonstrated | HbA1c $<7\%$: 64.5 vs 58.1\% ($P = NR$) HbA1c $\leq 6.5\%$: 35.5 vs 37.2\% ($P = NR$) | $-1.26$ vs $-1.48$ mmol/L, ($P = NR$) | NR | NR | Doc sympt, asympt | NR |

$^a$Mean change from study baseline to study end-point, except where indicated. In cases where the change from baseline values were not directly reported, estimates were determined by subtracting the end-point values from the baseline values; $^b$Change is the mean change from the end of the induction period to the end of each treatment period. asympt, asymptomatic hypoglycemia; BIAsp30, 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart; BIAsp70, 70% soluble insulin aspart, 30% protamine-crystallized insulin aspart; BMI, body mass index; CT.gov, ClinicalTrials.gov; doc, documented; FBG, fasting blood glucose; FPG, fasting plasma glucose; GLIM, glimepiride; HbA1c, glycated hemoglobin; LM25, 25% insulin lispro, 75% insulin lispro protamine suspension; LM50, 50% insulin lispro, 50% insulin lispro protamine suspension; LS, least squares; NPH, neutral protamine Hagedorn; NR, values not reported; NS, not significant; PPG, postprandial plasma glucose; SMBG, self-monitored blood glucose; SMPG, self-monitored plasma glucose; sympt, symptomatic hypoglycemia; undoc, undocumented.
in the study where patients were switched from premixed human insulin to a premixed insulin analog.

Of the eight studies reporting data, SMBG/SMPG concentrations were generally decreased from baseline for each assessment point during the day after treatment with premixed insulin analogs (Table 3; note: SMBG/SMPG results from these studies were typically focused on the comparison between treatment groups [see Table 3 for further details]).

In the 14 studies reporting data, doses were variable and were reported in IU/kg/day (9 studies) or IU/day (6 studies) among patients treated with premixed insulin analogs (Table 3). Doses ranged from 0.21 to 0.87 IU/kg/day and 17.8 to 53.99 IU/day among all studies, 0.21 to 0.87 IU/kg/day and from 17.8 to 38.6 IU/day in studies where patients received initiation of insulin, and 0.38 to 0.56 IU/kg/day and from 46.8 to 53.99 IU/day in studies where patients received intensification of insulin.

Safety outcomes

In 14 studies reporting data, the incidence of hypoglycemia was highly variable, ranging from 8.3 to 72.0% among all studies, 8.3 to 68.9% in studies where patients received initiation of insulin therapy, and 55 to 72.0% in studies where patients received intensification of insulin therapy (Table 3). In one study comparing high and low mixtures, the incidence of hypoglycemia was considerably higher, at up to 90%. The incidence of nocturnal hypoglycemia ranged from 0 to 47.2% among all studies. Severe/major hypoglycemia, where reported, was rare, ranging from 0 to 7% among all studies (0% in most studies). Unsurprisingly, the incidence of hypoglycemia was generally much higher in studies where assessment of hypoglycemia included undocumented hypoglycemia compared with studies where assessment only included documented hypoglycemia.

In all but one of the 14 studies reporting data, bodyweight/BMI increased from baseline to end-point after treatment with premixed insulin analogs; the increase was generally greater with insulin initiation than with insulin intensification. Mean/least squares mean bodyweight changes ranged from +0.62 to +4.09 kg among all 10 studies reporting data, +1.2 to +4.09 kg in studies where patients received initiation of insulin therapy, and +0.62 to +1.94 kg in studies where patients received intensification of insulin therapy. Mean BMI changes ranged from −0.3 to +6.1 kg/m² among the four studies reporting data.

Premixed insulin analogs vs Basal insulin

Two studies reported data comparing premixed insulin analogs with basal insulin. In the study reported by Lee et al., treatment with a premixed insulin analog (once or twice daily) was associated with more pronounced decreases from baseline in HbA1c and a slightly higher proportion of patients attaining the HbA1c target of ≤7% than treatment with basal insulin. In the study reported by Yang et al., treatment with a premixed insulin analog was found to be non-inferior to treatment with basal insulin on the basis of the HbA1c change from baseline. Other outcomes, including the incidence of hypoglycemia, were not significantly different between the two treatment groups.

Premixed insulin analogs vs Basal–bolus insulin

Seven studies reported data comparing premixed insulin analogs with basal–bolus insulin. In all of these studies, the change from baseline in HbA1c was, in general, not significantly different between the premixed insulin analog and basal–bolus groups, with one study showing non-inferiority on the basis of this comparison. Another showed a significantly greater decrease in HbA1c in the premixed insulin analog group compared with the basal–bolus group. Likewise, other outcomes, including the incidence of hypoglycemia and weight/BMI gain, were not significantly different between groups (or favored the premixed insulin analog group), except in the study reported by Hirao et al., where the increase in BMI was significantly greater in the premixed insulin analog group compared with the basal–bolus insulin group.

Premixed insulin analogs vs Premixed human insulin

Two studies reported data comparing premixed insulin analogs with premixed human insulin. In the study reported by Zhang et al., the change from baseline in HbA1c was numerically similar between groups; however, the incidence of hypoglycemia was numerically lower in the premixed insulin analog group compared with the premixed human insulin group. In the study reported by Yamada et al., the change from baseline to end-point in HbA1c was significantly greater in the premixed insulin analog group than in the premixed human insulin group. Other outcomes were numerically similar or not significantly different between groups.

Premixed insulin analogs: East Asian vs Caucasian

Two studies reported data for East Asian and Caucasian patients. In the study reported by Ji et al., there were no significant differences between races for any of the outcomes. However, numerical differences between races included the proportion of patients attaining the HbA1c target (higher in Caucasians), total daily insulin dose (lower in East Asians), the overall and nocturnal incidence of hypoglycemia (lower in East Asians), and bodyweight gain (lower in East Asians). In the study reported by Jeong et al., statistical comparisons were not made between the East Asian and Caucasian groups. The proportion of patients attaining HbA1c targets was numerically similar between East Asians and Caucasians. Numerical differences between races included the change from baseline to end-point in HbA1c (slightly more pronounced in East Asians), total daily insulin dose (lower in East Asians), the overall and nocturnal incidence of hypoglycemia (lower in East Asians), and bodyweight gain (lower in East Asians).
DISCUSSION
This is the first systematic review to examine the efficacy and safety of premixed insulin analogs in East Asians with type 2 diabetes. The results from the randomized controlled trials included in the present review show that premixed insulin analogs can improve glycemic control in the context of both initiation or intensification of insulin therapy. Furthermore, the magnitude of improvement and the safety profile appear to be similar to those associated with basal or basal–bolus insulin therapy. The evidence from studies reporting data for East Asians and Caucasians was limited, but suggests that dosing, efficacy and safety profiles of premixed insulin analogs might differ slightly as a result of race/ethnicity and/or cultural factors. Taken together, these results support the current use of premixed insulin analogs for managing type 2 diabetes in East Asians.

The results of the present systematic review show that premixed insulin analogs can improve glycemic control, regardless of the type of premixed insulin used, the ratio of rapid- to intermediate-acting insulin, the treatment regimen or the duration of treatment. Furthermore, the studies comparing premixed insulin analogs with other insulin treatments consistently showed that improvements in glycemic control were either numerically similar between groups or favored the premixed insulin analog group. These findings therefore suggest that premixed insulin analogs have an efficacy profile that is not different to those for other insulin treatments in East Asians with type 2 diabetes.

Consistent with the efficacy findings, the studies comparing premixed insulin analogs with other insulin treatments showed that the incidence of hypoglycemia and bodyweight/BMI gain were generally numerically similar between groups. These findings suggest that premixed insulin analogs have a safety profile that is not different to those for other insulin treatments in East Asians with type 2 diabetes. The findings from several studies involving primarily Caucasian populations show that hypoglycemia is more common with twice-daily premixed insulin than with basal insulin. None of the studies identified in the present review specifically compared these two regimens; hence, additional studies are required to determine if twice-daily premixed insulin increases the rate of hypoglycemia relative to basal insulin in East Asians with type 2 diabetes. Nevertheless, from the available evidence, the apparent similarities in efficacy and safety between premixed insulin analogs and other insulin treatments might reassure East Asian physicians and patients (e.g., patients with consistent daily routines, and/or those who prefer to avoid the burden of frequent blood glucose monitoring and/or injections) who are attracted to the possibility of less complicated regimens that premixed insulin analogs can provide.

The studies identified in the present systematic review consistently reported improvements in glycemic control after both initiation and intensification of insulin therapy with premixed insulin analogs. As expected, the improvements in glycemic control were generally greater for initiation vs intensification with premixed insulin analogs (and indeed comparator treatments). Likewise, bodyweight/BMI gain was greater for initiation vs intensification with premixed insulin analogs. Nevertheless, these findings support the use of premixed insulin analogs in both initiation and intensification of insulin therapy in East Asians.

There were several numerical differences in the efficacy and safety findings between East Asians and Caucasians treated with premixed insulin analogs. Specifically, total daily insulin dose, the overall and nocturnal incidence of hypoglycemia, and bodyweight gain were lower in East Asians than in Caucasians treated with premixed insulin analogs. In one study reporting data, the improvement in HbA1c was also slightly more pronounced in East Asians, whereas in the other study reporting data, the proportion of patients attaining the HbA1c target was higher among Caucasians. As both studies were post-hoc analyses, and therefore not sufficiently powered, statistical comparisons between races were generally not carried out. Some of the numerical differences might be at least in part explained by differences in dose between East Asians and Caucasians (e.g., those for hypoglycemia and bodyweight); however, race/ethnicity-related factors cannot be ruled out, and, therefore, might need to be considered in the prescription of premixed insulin analogs.

We acknowledge that our systematic review has a number of limitations. Specifically, there was, in some cases, considerable variability between studies in eligibility criteria, duration of treatment, type of treatment (both active and control) and treatment regimens. This variability limited the possibility for higher-level comparisons; for example, of outcomes by treatment duration and so on. Other limitations include the small sample size in some studies, the (generally unavoidable) lack of blinding in all studies, and the fact that just two studies compared efficacy and safety between East Asians and Caucasians. Furthermore, as the studies comparing outcomes between East Asians and Caucasians were subanalyses, the results must be seen as hypothesis-generating rather than conclusive. We restricted our review to studies comparing premixed insulin with traditional insulin therapies and did not include glucagon-like peptide-1 receptor agonists, which can be combined with basal insulin. However, to our knowledge, no published head-to-head studies have compared premixed insulin with basal insulin combined with a glucagon-like peptide-1 agonist in East Asians/Asians with type 2 diabetes. Therefore, the comparative efficacy and safety of these regimens is yet to be confirmed. Finally, we did not identify any eligible studies reporting on the use of the newly available insulin analog mix, insulin degludec/insulin aspart, in East Asians with type 2 diabetes. A pan-Asian study of patients with type 2 diabetes showed that changes in HbA1c and rates of hypoglycemia after 26 weeks of treatment with BIAsp or insulin degludec/insulin aspart were not significantly different between treatment groups, whereas FPG control...
was significantly better among patients treated with insulin degludec/insulin aspart\textsuperscript{39}. Nevertheless, the present systematic review does have a number of noteworthy strengths, including that all studies were randomized controlled trials considered to have a low or unclear risk of bias for most categories, the lack of language restrictions, the inclusion of all types of premixed insulin analogs, and the inclusion of studies on both the initiation and intensification of insulin therapy.

In conclusion, the results of the present systematic review highlight that premixed insulin analogs can be a simple and effective means of treating type 2 diabetes in East Asians, with a safety profile that is generally similar to that of basal and basal–bolus insulin. Clearly, management of type 2 diabetes should always be customized on a patient-by-patient basis. To this end, treatment with premixed insulin analogs might be particularly well suited to certain East Asian patients who prefer a less complex regimen than those required for some other insulin treatments.

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**DISCLOSURE**

WHHS has received speaker honorariums and served as a scientific advisor board member for Merck Sharp & Dohme, Bristol-Myers Squibb, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Sanofi, Takeda, Astra-Zeneca and Bayer. LJ has served as a consultant for Eli Lilly. WJL has served as a consultant for AstraZeneca, Daewoong, Servier, Sanofi-Aventis, Merck Sharp & Dohme, Takeda, Novartis and JW Pharmaceutical. AJ, JHH and TL are employees of Eli Lilly. AJ and TL own shares in Eli Lilly.

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