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ORIGINAL ARTICLE

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 2040[1]. 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 decades[2]. 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 diabetes[3–7]. 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 Caucasians[8,9]. 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.

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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 insulin[10], and approximately one-third of Japanese patients initiate insulin therapy with premixed insulin[11]. Despite the wide (and recommended[12,13]) 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[14].

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[15,16] that had been submitted, but not published at the time of the literature search); hence, 18 studies[15–32] from the literature were included in the review. Three eligible studies[33–35] were identified in the search of ClinicalTrials.gov and included.

Study characteristics

Most studies (n = 14)[15,17–20,22–26,28,30,33–35] were carried out in China or Japan; there were four multicountry studies[15,16,21,32] (Table 1).

The studies were generally similar in design, but of variable duration (Table 1). All had parallel treatment arms, except for one study[18] 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 (n = 15)[15–17,21–23,25,27,29–35] included patients with a minimum HbA1c of ≥7.0 or ≥7.5% (Table 1). One study[18] 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)[15,17–27,31,33], rather than intensification (six studies)[16,28–30,32,35], of insulin therapy (Table 1). In one study, patients were switched from premixed human insulin to a premixed insulin analog[34].

Premixed insulin analogs used in the studies included the low mixtures 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart (BIAsp30, 12 studies[19–21,24–27,29–31,34,35]); 25% insulin lispro, 75% insulin lispro protamine suspension (LM25, six studies[15,16,22,23,32,33]); the mid mixture 50% insulin lispro, 50% insulin lispro protamine suspension (LM50, seven studies[17,18,22–24,28,32]); and the high mixture 70% soluble insulin aspart, 30% protamine–crystallized insulin aspart (BIAsp70, one study[30]; Table 1). Several studies included more than one premixed insulin analog treatment group. Control/comparator interventions included basal–bolus insulin (seven studies[15–17,19,20,29,32]), basal insulin (two studies[21,31]) and premixed human insulin (two studies[18,28]). Different premixed insulin analogs or premixed insulin analog treatment regimens were compared in nine studies[22–27,30,34,35].

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

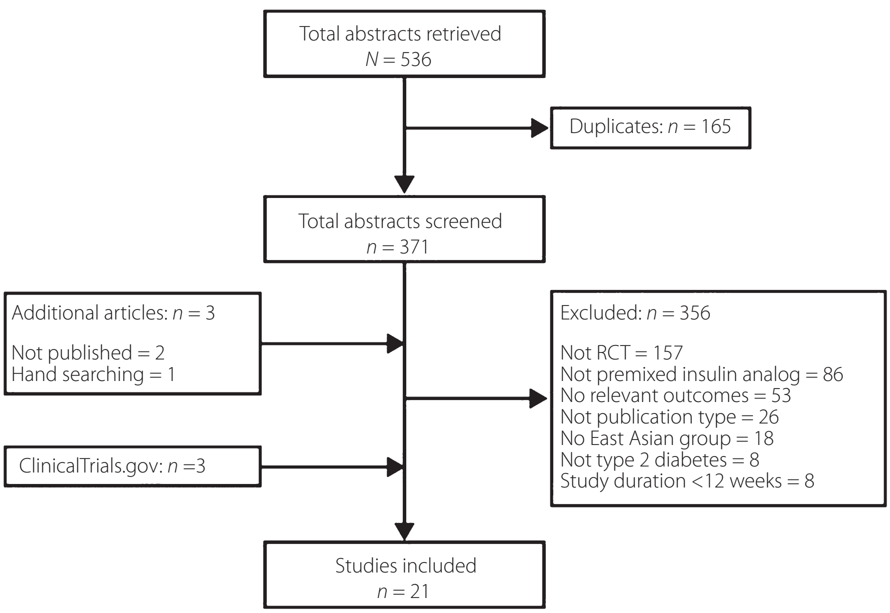

Figure 1 | Literature search flow diagram.

Table 1 | Summary of study characteristics

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
Initiation of insulin therapy						
Masuda (2008)[17] Japan	R, OL 12 weeks	HbA1c ≥7.0%, insulin naïve	OADs	LM50 (n = 14) NPH insulin + insulin lispro (n = 14)	LM50 twice daily NPH insulin at bedtime + preprandial 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	NR
Ji (2016)[15] China, Korea	R, OL 48 weeks	HbA1c ≥7.0 and ≤11.0%, insulin naïve	OADs	LM25 East Asian (n = 45) Caucasian (n = 69) Insulin glargine + insulin lispro East Asian (n = 44) Caucasian (n = 61) Continuation of OADs (all patients)	LM25 once daily before dinner, progressing to thrice daily (doses titrated to achieve FBG/pre-evening meal BG 4.5–6.0 mmol/L) 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)	Eli Lilly
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) Premixed human insulin 70/30 (n = 30) MET (obese patients only)	Induction (10 days) All patients: Premixed human insulin 70/30 (starting dose: 0.5–0.6 IU/kg) 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)	NR
Miyashita (2008)[19] Japan	R, OL 6 months	HbA1c ≥8.0	OADs	BIAsp30 (n = 21) NPH insulin + insulin aspart (n = 21) Continuation of MET and TZDs (all patients)	BIAsp30 before breakfast and dinner NPH insulin + insulin aspart at night on an on-demand basis 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%	NR

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)[20] Japan	R, OL 6 months	HbA1c ≥8.0, insulin naïve	OADs	BIAsp30 (*n* = 80) Insulin aspart ± NPH insulin (*n* = 80)[†]	BIAsp30 twice daily Insulin aspart thrice daily[‡] All doses titrated to achieve HbA1c <7.0%	Japan Diabetes Foundation
Lee (2011)[31] 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)	Once daily (doses titrated to achieve fasting glucose <6.1 mmol/L without significant hypoglycemia) 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 and 2 h postprandial glucose of 10 mmol/L, without significant hypoglycemia)	Yonsei University College of Medicine
Yang (2013)[21] 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	Novo Nordisk
Zafar (2015)[22] 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 ≥4.4 and ≤6.1 mmol/L)	Ministry of Education, People's Republic of China
Su (2015)[23] China	R, OL 26 weeks	HbA1c ≥7.0 and ≤11.0%	OADs	LM25 (*n* = 80) LM50 (*n* = 76)	Before breakfast & dinner (doses titrated to achieve FBG >3.9 and ≤6.1 mmol/L)	Eli Lilly
NCT01147627[33] China	R, OL 48 weeks	HbA1c 7.0–10.0%, drug treatment naïve	None	LM25 (*n* = 138)[§]	Before breakfast and dinner (50:50%) Doses titrated following a forced schedule per BG before breakfast and dinner	Sun Yat-sen University
Domeki (2014)[24] 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)[25] 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

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
Ebato (2009)[26] Japan	R, OL 48 weeks	HbA1c >8.0%, insulin naïve	OADs	BIAsp30 + GLIM (*n* = 14) BIAsp30 (*n* = 12) Continuation of OADs (all patients)	Week 1–24 BIAsp30 before breakfast (4 U, from week 8 onwards, +2 U if before dinner BG ≥200 mg/dL at week 10, titrated to achieve before dinner BG 121–180 mg/dL from week 11–24) GLIM 3 mg/day Week 25–48¶ BIAsp30 before breakfast & dinner (doses titrated to achieve before dinner & before breakfast BG, respectively, 101–150 mg/dL) ± GLIM 3 mg/day	Novo Nordisk
Jung (2014)[27] Korea	R, OL 24 weeks	HbA1c ≥7.5%, insulin naive	OADs	BIAsp30 (morning : evening ratio) 50:50% (*n* = 33) 55:45% (*n* = 34) 60:40% (*n* = 33) Continuation of OADs, except SU (all patients)	Before breakfast & dinner (doses titrated to achieve preprandial BG ≥4.4 and ≤6.1 mmol/L)	NR
Intensification of insulin therapy						
Yamada (2007)[28] Japan	R, OL 4 months	HbA1c >6.5%, treatment with 70/30 or 50/50 premixed insulin twice daily for ≥3 months	Premixed human insulin	LM50 (*n* = 15) Premixed human insulin (*n* = 15)	LM50 twice daily Premixed human insulin twice daily All doses titrated to achieve postprandial BG <180 mg/dL and FBG <130 mg/dL	NR
Jia (2015)[32] China, Taiwan, Korea	R, OL 24 weeks	HbA1c 7.0–12.0% on twice-daily premixed insulin	Premixed insulin ± OADs	LM50 + LM25 (*n* = 197) Insulin glargine + insulin lispro (*n* = 202) Continuation of OADs (all patients)	LM50 before breakfast & lunch + LM25 before dinner Insulin glargine at bedtime + insulin lispro before each meal All doses titrated to achieve preprandial BG <6.1 mmol/L and 2 h postprandial BG <7.8 mmol/L without hypoglycemia	Eli Lilly
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 East Asian (*n* = 40) Caucasian (*n* = 136) Insulin glargine + insulin lispro East Asian (*n* = 40) Caucasian (*n* = 143) MET and/or PIO (all patients)	LM25 before breakfast & dinner (doses adjusted to achieve FBG or predinner plasma-equivalent BG <6.1 mmol/L) Insulin glargine at bedtime (doses adjusted to achieve premeal plasma-equivalent BG 5.6-6.7 mmol/L) + insulin lispro before main meal (doses adjusted to achieve plasma-equivalent FBG ≤5.5 mmol/L)	Eli Lilly

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
Jin (2015)[29] 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 glargine 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)[30] Japan	R, OL, non-inferiority 28 weeks	HbA1c between 7.5 and 10.0%	Intermediate-acting, long-acting human, and/or premixed human insulin	BIAsp70 (n = 145) BIAsp30 (n = 144)	BIAsp70 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[35] 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 67:33% (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						
NCT01618214[34] China	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-crystallised insulin aspart; BIAsp70, 70% soluble insulin aspart, 30% protamine-crystallized insulin aspart; CT.gov, ClinicalTrials.gov; 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; TZD, 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[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[17,18,22–24,27,34], and increased from baseline to end-point in three studies[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[17,18,22–24,27] where patients received initiation of insulin therapy, increased from baseline in three studies[16,28,29] where patients received intensification of insulin therapy, and decreased from baseline

Table 2 | Risk of bias assessment

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)[17]	?	+	–	?	+	+	+
Ji (2016)[15]	+	+	–	?	+	+	+
Zhang (2010)[18]	?	?	–	?	?	?	?
Miyashita (2008)[19]	+	?	–	+	+	+	+
Hirao (2009)[20]	?	?	–	+	+	+	+
Lee (2011)[31]	?	?	–	?	+	+	+
Yang (2013)[21]	?	?	–	?	+	+	+
Zafar (2015)[22]	?	?	–	?	+	+	+
Su (2015)[23]	+	+	–	?	+	+	+
NCT01147627[33]	?	?	–	?	+	+	+
Domeki (2014)[24]	?	?	–	?	+	+	+
Yang (2008)[25]	+	+	–	?	+	+	+
Ebato (2009)[26]	?	?	–	?	+	+	+
Jung (2014)[27]	+	+	–	+	+	+	+
Yamada (2007)[28]	+	+	–	?	+	+	+
Jia (2015)[32]	+	+	–	+	+	+	+
Jeong (2016)[16]	+	+	–	?	+	+	+
Jin (2015)[29]	+	+	–	?	+	+	+
Kadowaki (2010)[30]	?	?	–	?	+	+	+
NCT01618214[34]	?	?	–	?	+	+	+
NCT01278160[35]	?	?	–	?	+	+	+

+ Low risk; ? unclear risk; – high risk.

Table 3 | Summary of study outcomes

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†
Initiation of insulin therapy							
Masuda (2008)[17] LM50 vs NPH insulin + insulin lispro	−4.2 vs −4.4% (P = NR)	NR	FPG −151 vs −171 mg/dL (P = NR)	NR	0.40 vs 0.45 IU/kg (P = NS)	Not defined NR (P = NS for rate/patient)	BMI −0.3 vs +0.2 kg/m^2(P = NS at baseline or end-point)
Ji (2016)[15] LM25 vs insulin glargine + insulin lispro	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 = NR 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%	Bodyweight East Asian: +2.95 vs +2.81 kg Caucasian: +3.00 vs + 3.43 kg P = NR for East Asian vs Caucasian
Zhang (2010)[18] LM50 vs premixed human insulin	Week 12 −1.72 vs −1.56% Week 24 −0.16 vs +0.02%	NR	FBG‡ 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 9.9 events; week 24, 3.5 vs 6.8 events)	NR
Miyashita (2008)[19] BIAsp30 vs NPH insulin + insulin aspart	−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)	NR	NR

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†
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 Major: 0 vs 0% episodes	BMI +1.47 vs +0.69 kg/m^2 (*P* = 0.013)
Lee (2011)[31] BIAsp30 once daily vs insulin detemir 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 2 h postdinner, bedtime, & 02.00–04.00 h significantly reduced (*P* < 0.05) for BIAsp30 vs insulin glargine; before dinner significantly reduced for insulin glargine vs BIAsp30 (*P* = 0.003)	17.8 vs 18.2 IU (*P* = NR)	Doc/undoc sympt, asympt Overall: 59.4 vs 56.9% (*P* = NR) Nocturnal: 18.8 vs 15.0% (*P* = NR) Severe: 0 vs 0.4% (*P* = NR)	Bodyweight +1.2 vs +1.4 kg (*P* = 0.548)
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 Minor: 6.84 vs 5.48% (*P* = NS) Nocturnal: 0 vs 2.74% (*P* = NS) Major: 0 vs 0%	Bodyweight +1.92 vs +2.03 (*P* = NS)
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 Predinner, postdinner & bedtime significantly reduced (*P* < 0.05) for LM50 vs LM25	38.6 vs 36.2 IU (*P* = NS)	Doc/undoc sympt, asympt Overall: 48.8 vs 48.7% (*P* = NR) Nocturnal: 13.8 vs 7.9% (*P* = NR) Severe: 0 vs 0%	LS mean Bodyweight +1.6 vs +1.5 kg (*P* = NS)
NCT01147627[33] LM25	−1.74%	NR	NR	NR	NR	NR	NR

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 Overall: 8.3 vs 8.3% Severe: 0 vs 0%	BMI +2.7 vs +6.1 kg/m^2 (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 ≤6.5%: 34.4 vs 46.6% (P < 0.05)	NR	NR	0.82 vs 0.86 IU/kg (P = 0.19)	Doc sympt 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 8.3% (P = NR)	NR	NR	0.21 vs 0.36 IU/kg (P < 0.05)	Doc sympt, asympt 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%: 29.6 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	0.45 vs 0.46 vs 0.54 IU/kg (P = 0.142)	Doc sympt Overall: 51.6 vs 50.0 vs 53.3% (P = 0.965)	Bodyweight +1.72 vs +0.93 vs +1.89 kg (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	0.38 vs 0.37 IU/kg (P = NS)	Severe: 0 vs 0%	BMI +0.3 vs −0.2 kg/m^2 (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 ≤6.5%: 9.1 vs 11.9% (P = NR)	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)	52.93 vs 53.99 IU (P = 0.106)	Not defined Overall: 55 vs 55% (P = 0.148 for rate/30 days) Nocturnal: 14 vs 11% (P = 0.235 for rate/days) Severe: 0 vs 0%	Bodyweight +0.8 kg vs +0.7 kg (P = NR)

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†
Jeong (2016)[16] LM25 vs insulin glargine + insulin lispro	East Asian −1.3 vs −0.9% ($P < 0.001$) Caucasian −1.2 vs −1.0% ($P < 0.001$)	HbA1c <7% East Asian: 33.3 vs 22.9% (P = NS) Caucasian: 37.2 vs 34.1% (P = NS) HbA1c ≤6.5% East Asian: 17.9 vs 5.7% (P = NR) Caucasian: 16.5 vs 17.1% (P = NR)	FBG East Asian: 0.40 vs 0.25 mmol/L (P = NS) Caucasian: 0.87 vs 0.74 mmol/L ($P \leq 0.01$)	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) Caucasian: 0.69 vs 0.67 IU/kg (P = NR)	Doc sympt *Overall* East Asian: 65.0 vs 82.1% (P = NR) Caucasian: 69.9 vs 64.1% (P = NR) *Nocturnal* East Asian: 17.5 vs 17.9% (P = NR) Caucasian: 22.8 vs 25.4% (P = NR) *Severe* East Asian: 0 vs 0% Caucasian: 0.7 vs 0% (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 (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†
Kadowaki (2010)[30] BIAsp70 vs BIAsp30	−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 Overall: 90.3 vs 88.2% (P = NS) Nocturnal: 27.8 vs 47.2% ($P < 0.001$) Major: 0.7 vs 2.1% (P = NS)	Bodyweight +1.94 vs + 1.23 kg ($P = 0.011$)
NCT01278160[35] BIAsp30: 2/3 and 1/3 split vs 1/2 and 1/2 split	LS mean −0.13 vs −0.12	HbA1c <7%: 12.4 vs 14.4% ($P = 0.731$) HbA1c ≤6.5%: 2.2 vs 7.8% ($P = 0.126$)	NR	9-point SMPG No significant differences between groups at any time-point	NR	Doc sympt, asympt NR (P = NS for overall, nocturnal & severe no. episodes)	NR
Switch from premixed human insulin							
NCT01618214[34] BIAsp30: patient-driven vs investigator-driven titration	−1.32 vs −1.31% Non-inferiority demonstrated	HbA1c <7%: 64.5 vs 58.1% (P = NR) HbA1c ≤6.5%: 35.5 vs 37.2% (P = NR)	−1.26 vs −1.48 mmol/L (P = NR)	NR	NR	Doc sympt, asympt NR (rate/year similar for overall and severe)	NR

†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; ‡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[34] where patients were switched from premixed human insulin to a premixed insulin analog.

Of the eight studies[16,19,21,23,29,30,32,35] 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[15–17,19,22,25–28]) or IU/day (6 studies[15,18,21,23,30,32]) 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[15,16,20–30,32] 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[30], 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[17] of the 14 studies[15–17,20–25,27–30,32] 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[15,16,21–23,25,27,29,30,32] 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/m^2 among the four studies[17,20,24,28] reporting data.

Premixed insulin analogs vs Basal insulin

Two studies[21,31] reported data comparing premixed insulin analogs with basal insulin. In the study reported by Lee *et al.*[31], 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.*[21], 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[15–17,19,20,29,32] 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[32]. Another showed a significantly greater decrease in HbA1c in the premixed insulin analog group compared with the basal–bolus group.[16] 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.*[20], 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[18,28] reported data comparing premixed insulin analogs with premixed human insulin. In the study reported by Zhang *et al.*[18], 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.*[28], 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[15,16] reported data for East Asian and Caucasian patients. In the study reported by Ji *et al.*[15], 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.*[16], 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[36–38]. 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[16] reporting data, the improvement in HbA1c was also slightly more pronounced in East Asians, whereas in the other study[15] 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[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.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels: International Diabetes Federation, 2015.
2. Ramachandran A, Snehalatha C, Shetty AS, *et al.* Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; 3: 110–117.
3. Davidson JA, Lacaya LB, Jiang H, *et al.* Impact of race/ethnicity on the efficacy and safety of commonly used insulin regimens: a post hoc analysis of clinical trials in type 2 diabetes mellitus. *Endocr Pract* 2010; 16: 818–828.
4. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care* 2011; 34: 1249–1257.
5. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. *Lancet* 2010; 375: 408–418.
6. Ramachandran A, Snehalatha C, Vijay V. Low risk threshold for acquired diabetogenic factors in Asian Indians. *Diabetes Res Clin Pract* 2004; 65: 189–195.
7. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
8. Wang JS, Tu ST, Lee IT, *et al.* Contribution of postprandial glucose to excess hyperglycaemia in Asian type 2 diabetic patients using continuous glucose monitoring. *Diabetes Metab Res Rev* 2011; 27: 79–84.
9. Dickinson S, Colagiuri S, Faramus E, *et al.* Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. *J Nutr* 2002; 132: 2574–2579.
10. Ji LN, Lu JM, Guo XH, *et al.* Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. *BMC Public Health* 2013; 13: 602.
11. Freemantle N, Balkau B, Danchin N, *et al.* Factors influencing initial choice of insulin therapy in a large international non-interventional study of people with type 2 diabetes. *Diabetes Obes Metab* 2012; 14: 901–909.
12. Chinese Diabetes Society. China Guideline for Type 2 Diabetes. Beijing: Chinese Diabetes Society, 2013.
13. Diabetes Association of the R.O.C. DAROC Clinical Practice Guidelines for Diabetes Care - 2015. Taipei: Diabetes Association of the R.O.C, 2015.
14. Higgins JP, Altman DG, Gotzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
15. Ji L, Min KW, Lei Y, *et al.* Comparison of efficacy and safety of two insulin regimens in Caucasian, Western Asian and Eastern Asian patients with type 2 diabetes: a post hoc analysis of the PARADIGM study. *Diabetes Metab Syndr Obes* 2016; 9: 243–249.
16. Jeong I, Chung CH, Zhou Z, *et al.* Comparison of insulin intensification strategies with insulin lispro low mixture twice daily versus basal insulin glargine and prandial insulin lispro once daily in East Asian and Caucasian patients with type 2 diabetes mellitus. *J Diabetes* 2016. doi: 10.1111/1753-0407.12426.
17. Masuda H, Sakamoto M, Irie J, *et al.* Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naive type 2 diabetic patients. *Diabetes Obes Metab* 2008; 10: 1261–1265.
18. Zhang AM, Li CW. Efficacy of mixed protamine zinc recombinant human insulin lispro injection (50R) in 60 patients with type 2 diabetes mellitus. *Chin J New Drugs* 2010; 19: 509–512.
19. Miyashita Y, Nishimura R, Nemoto M, *et al.* Prospective randomized study for optimal insulin therapy in type 2

diabetic patients with secondary failure. *Cardiovasc Diabetol* 2008; 7: 16.
20. Hirao K, Arai K, Yamauchi M, *et al.* Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). *Diabetes Res Clin Pract* 2008; 79: 171–176.
21. Yang W, Xu X, Liu X, *et al.* Treat-to-target comparison between once daily biphasic insulin aspart 30 and insulin glargine in Chinese and Japanese insulin-naive subjects with type 2 diabetes. *Curr Med Res Opin* 2013; 29: 1599–1608.
22. Zafar MI, Ai X, Shafqat RA, *et al.* Effectiveness and safety of Humalog Mix 50/50 versus Humalog Mix 75/25 in Chinese patients with type 2 diabetes. *Ther Clin Risk Manag* 2015; 11: 27–32.
23. Su Q, Qian L, Li P, *et al.* Insulin mid mixture lispro mix50 (LM50) showed better glycemic control than low mixture lispro mix 25 (LM25) as starter insulin in Chinese patients with type 2 diabetes mellitus (T2DM): A subgroup analysis of CLASSIFY study. 75th Scientific Sessions of the American Diabetes Association Boston, MA, USA 2015; A268.
24. Domeki N, Matsumura M, Monden T, *et al.* A randomized trial of step-up treatment with premixed insulin lispro-50/50 vs. aspart-70/30 in patients with type 2 diabetes mellitus. *Diabetes Ther* 2014; 5: 403–413.
25. Yang W, Ji Q, Zhu D, *et al.* Biphasic insulin aspart 30 three times daily is more effective than a twice-daily regimen, without increasing hypoglycemia, in Chinese subjects with type 2 diabetes inadequately controlled on oral antidiabetes drugs. *Diabetes Care* 2008; 31: 852–856.
26. Ebato C, Shimizu T, Arakawa M, *et al.* Effect of sulfonylureas on switching to insulin therapy (twice-daily biphasic insulin aspart 30): comparison of twice-daily biphasic insulin aspart 30 with or without glimepiride in type 2 diabetic patients poorly controlled with sub-maximal glimepiride. *Diabetes Res Clin Pract* 2009; 86: 31–36.
27. Jung CH, Park JY, Cho JH, *et al.* The optimal morning: evening ratio in total dose of twice-daily biphasic insulin analogue in poorly controlled Type 2 diabetes: a 24-week multi-centre prospective, randomized controlled, open-labelled clinical study. *Diabet Med* 2014; 31: 68–75.
28. Yamada S, Watanabe M, Kitaoka A, *et al.* Switching from premixed human insulin to premixed insulin lispro: a prospective study comparing the effects on glucose control and quality of life. *Intern Med* 2007; 46: 1513–1517.
29. Jin SM, Kim JH, Min KW, *et al.* Basal-prandial versus premixed insulin in patients with type 2 diabetes requiring insulin intensification after basal insulin optimization: a 24-week randomized non-inferiority trial. *J Diabetes* 2016; 8: 405–413.
30. Kadowaki T, Nishida T, Kaku K. 28-week, randomized, multicenter, open-label, parallel-group phase III trial to investigate the efficacy and safety of biphasic insulin aspart 70 thrice-daily injections vs twice-daily injections of biphasic insulin aspart 30 in patients with type 2 diabetes. *J Diabetes Investig* 2010; 1: 103–110.
31. Lee YH, Lee BW, Chun SW, *et al.* Predictive characteristics of patients achieving glycaemic control with insulin after sulfonylurea failure. *Int J Clin Pract* 2011; 65: 1076–1084.
32. Jia W, Xiao X, Ji Q, *et al.* Comparison of thrice-daily premixed insulin (insulin lispro premix) with basal-bolus (insulin glargine once-daily plus thrice-daily prandial insulin lispro) therapy in east Asian patients with type 2 diabetes insufficiently controlled with twice-daily premixed insulin: an open-label, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2015; 3: 254–262.
33. National Institute of Mental Health; University of Virginia. Effect of different interventions on glycemic control and β-cell function in newly diagnosed type 2 diabetic patients. Bethesda (MD): National Library of Medicine (US). Available from https://clinicaltrials.gov/ct2/show/NCT01147627 Accessed November 26, 2016.
34. National Institute of Mental Health; University of Virginia. Comparison of subject-driven titration of biphasic insulin aspart (BIAsp) 30 twice daily versus investigator-driven titration of BIAsp 30 twice daily both in combination with oral antidiabetic drugs in subjects with type 2 diabetes. Bethesda (MD): National Library of Medicine (US). Available from https://clinicaltrials.gov/ct2/show/NCT01618214 Accessed November 26, 2016.
35. National Institute of Mental Health; University of Virginia. Comparison of biphasic insulin aspart 30 twice daily with two different initial dosage split regimens in subjects with type 2 diabetes: An extension to trial BIASP-3756. Bethesda (MD): National Library of Medicine (US). Available from https://clinicaltrials.gov/ct2/show/NCT01278160 Accessed November 26, 2016.
36. Holman RR, Thorne KI, Farmer AJ, *et al.* Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007; 357: 1716–1730.
37. Janka HU, Plewe G, Riddle MC, *et al.* Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 2005; 28: 254–259.
38. Raskin P, Allen E, Hollander P, *et al.* Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005; 28: 260–265.
39. Kaneko S, Chow F, Choi DS, *et al.* Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre-/self-mixed insulin: a 26-week, randomised, treat-to-target trial. *Diabetes Res Clin Pract* 2015; 107: 139–147.