Comparative efficacy and safety of long-acting insulin analogs in patients with type 2 diabetes failing on oral therapy: Systemic review and meta-analyses

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ABSTRACT

Aims/Introduction: Although long-acting insulin analogs are recommended in type 2 diabetics failing on oral agents, their efficacy is uncertain. Here we compared the efficacy and safety of regimens based on long-acting insulin analogs with other preparations in insulin-naïve type 2 diabetics failing on oral agents.

Materials and Methods: Data from 9548 participants in 22 English studies were included. Most of the studies were of short to medium duration and of low quality.

Results: In terms of decreasing hemoglobin A1c, long-acting insulin analogs were not statistically significant to rapid-acting insulin analogs or intermediate neutral protamine Hagedorn (NPH) insulin or glucagon-like peptide-1 (GLP-1) analogs, and the differences between long-acting and biphasic insulin analogs were marginal. Compared with rapid-acting insulin analogs, long-acting insulin analogs were similar in the incidence of total hypoglycemia, and the superiority in less weight gain was inconsistent. Relative to biphasic insulin analogs, long-acting insulin analogs were associated with lower incidence of total hypoglycemia and less weight gain. Compared with NPH insulin, long-acting insulin analogs were associated with lower incidence of total and nocturnal hypoglycemia. Relative to GLP-1 analogs, long-acting insulin analogs were associated with lower incidence of treatment related adverse events but with greater weight gain.

Conclusions: For type 2 diabetics failing on oral agents, initiating long-acting insulin analogues seems to provide glycemic control similar to rapid-acting insulin analogs or NPH insulin or glucagon-like peptide-1 analogs and slightly inferior to biphasic insulin analogs with fewer side-effects. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00187.x, 2012)

KEY WORDS: Long-acting insulin analogs, Meta-analysis, Type 2 diabetes

INTRODUCTION

The landmark prospective randomized clinical trials (RCT) from the UK Prospective Diabetes Study (UKPDS) showed that improving glycemic control, as assessed by hemoglobin A1c (HbA_{1c}) levels, reduces the risks of complications in type 2 diabetes[1–3]. To achieve adequate glycemic control, many type 2 diabetics after failing on oral hypoglycemic agents (OHA) will eventually require insulin therapy as deterioration of β-cell function and loss of β-cell mass progresses over time[4,5]. Recent American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus statements recommend the early initiation of basal insulin therapy as a result of their simplicity and feasibility, combined with OHA in patients not achieving acceptable glucose control[6]. The two available long-acting insulin analogs, including insulin glargine and insulin detemir, have been designed to provide more consistent, relative flat and protracted basal insulin levels than intermediate-acting insulin[7].

However, there is a general uncertainty as to whether basal insulin based on regimens will help as many patients achieve glycemic control as biphasic insulin and rapid-acting insulin preparations based on regimens[8,9]. Initial 1-year data from the Treating-to-Target in Type 2 diabetes (4-T) study showed that less than one-third of patients who were assigned to receive the long-acting insulin analog to oral therapy reached a HbA_{1c} level below the recommended 7% target, which was lower than that of the biphasic and rapid-acting insulin analog[10]. Previous meta-analyses studies found that HbA_{1c} reduction might be obtained in type 2 diabetes when insulin is initiated with biphasic or

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prandial insulin regimens rather than basal regimens[8,9]. Nevertheless, after those publications, further results after 3-year follow up from the 4-T study have been published, in which they reported patients who added to a long-acting insulin analog or rapid-acting insulin analog-based regimens achieved better glycemic control than a biphasic insulin analog-based regimen[11].

Therefore, the optimal insulin regimen to start with when OHA fails to control glucose in type 2 diabetes is far more uncertain[8,9,12]. In the present study, we present up-to-date data from a systemic review and meta-analyses of RCT, which aimed to assess the comparative effectiveness and safety of regimens based on long-acting insulin analogs compared with other injectable preparations in insulin-naïve patients with type 2 diabetes failing on oral agents.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

We included RCT if they reported data for comparing long-acting insulin analog-based regimens vs one of the following injectable agents-based regimens – rapid-acting insulin analogs, or biphasic insulin analogs, or NPH insulin, or glucagon-like peptide-1 (GLP-1) analogs – with a duration of 12 weeks or longer, and recruited insulin-naive adults (>18 years) with type 2 diabetes inadequately controlled with oral agents. Pooled analyses on human biphasic insulin or intermediate-acting insulin analog were not possible, because only one study for each comparison was reported. We limited the research to English-language studies; non-English-language studies were excluded, because the quality of these studies is difficult to evaluate. If we identified more than one publication of an original study, we assessed those articles together to maximize data collection. Citations were excluded if: (i) the intervention time was <12 weeks; (ii) the use of OHA was unbalanced between study arms; (iii) they related to type 1 diabetes; or (iv) there was a history of insulin treatment.

Outcome Measures

In the present study, we present results for intermediate clinical outcomes of HbA_{1c}; fasting glucose; postprandial glucose; weight gain; daily insulin dose by bodyweight; the incidence of total, nocturnal and severe hypoglycemia; and the incidence of any adverse events, treatment-related adverse events and withdrawal as a result of adverse events.

Search Strategy

We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (1980 to March 2010) to identify relevant RCT trials using terms of type 2 diabetes, long-acting insulin, detemir or levemir, glargine or lantus.

Data Extraction and Study Quality Assessment

Two investigators independently reviewed relevant publications and abstracted the data, and any disagreements were resolved by consensus and discussion with a third reviewer. Methodological quality was assessed using criteria set out by Jadad[13], with an additional point given if the analysis was by intention-to-treat[8].

Data Synthesis and Statistical Analysis

Data were combined by using a random-effects model (Review Manager Version 4.2.10; The Cochrane Collaboration, Copenhagen, Denmark). For the evaluation of outcomes, we combined parallel and crossover trials, because no crossover studies reported carryover effects. Data from intention-to-treat studies were recorded after intention-to-treat principles.

For the evaluation of outcomes of HbA_{1c}, fasting, postprandial glucose and weight gain, the changes between baseline and end-point were used for the comparisons between groups. Standard deviation (SD) was recorded from studies or calculated from the baseline, and final SD using a correlation of 0.5 or from 95% confidence intervals (CI) and *P*-values for the difference in means (Cochrane Collaboration, 2004). Definitions of hypoglycemia varied among studies (Table 1). The most consistently reported measure of hypoglycemia was the percentage of participants experiencing an episode of a specific type of hypoglycemia (symptomatic, asymptomatic, nocturnal and severe). Therefore, we chose to combine this measure by calculating the incidence of participants experiencing an episode of a specific type for each intervention as an overall indicator of hypoglycemia.

Continuous outcomes were calculated by weighted mean differences (WMD) with 95% CI. Dichotomous outcomes were summarized as odds ratio (OR) with 95% CI. We determined heterogeneity by using an I^2 statistic[14], and we carried out subgroup analysis for: (i) baseline HbA_{1c} (<9%, ≥9%; as the failure criteria used in different studies); (ii) quality score (<3, ≥3); (iii) variation in study length; (iv) oral agents given as added-on therapy (yes or not) or the nature of the oral agents used in combination with insulin; and (v) long-acting insulin analogs (glargine, detemir). We carried out sensitivity analyses to determine whether inclusion of studies deemed to be of low methodological quality affected the results. Funnel plots were used to assess the potential for publication bias and small sample size.

RESULTS

Study Characteristics

In total, data from 9548 participants in 22 RCT studies were included (Figure 1). A total of 19 were parallel groups and three were crossovers. A total of 17 studies were analyzed according to intention-to-treat principles. A total of 15 studies described randomization methods[11,15,17,18,20,25–30,32–35]. No study was double-blinded. The median quality score of included studies was 3. The study participants had a mean age of 57.7 years, mean body mass index of 30.1 kg/m^2, mean duration of diabetes of 9.0 years, and 55.6% were male. The median duration of follow up was 34 weeks, and average study size was 434 participants. Participants had a median HbA_{1c} level of 8.8%, and median fasting plasma glucose of 10.9 mmol/L. A total of 20 studies

Table 1 | Characteristics of included studies

Author, Year, Reference	Groups	Study length (weeks)	Patients (*n*)	Men (%)	Mean age (years)	Mean BMI (kg/m^2)	Diabetes duration (years)	Start HbA_{1c} (%)	Start FPG (mmol/L)	Hypoglycemia (<mmol/L)	Previous treatment	Quality score
Long-acting insulin analogs vs rapid-acting insulin analogs												
Holman 2009[11]	Detemir vs aspart, SU was replaced by second insulin if necessary	148	473	62.4	61.8	29.7	9	8.5	9.6	3.1	MET+SU	4
Bretzel 2008[15] (intention-to-treat)	Glargine vs lispro, both plus previous OHA	44	377	57	59.7	29.25	8.85	8.7	10.1	3.3	MET/SU/TZD/ α-Glucosidase inhibitors	4
Kazda 2006[16]	Glargine vs lispro	24	105	52.5	59.8	30.4	5.4	8.2	9.7	3	MET/SU/TZD/ α-Glucosidase inhibitors/Glinides	3
Long-acting insulin analogs vs biphasic insulin analogs												
Holman 2009[11]	Detemir vs BIAsp70/30, SU was replaced by second insulin if necessary	148	469	64.5	61.8	30.0	9	8.5	9.6	3.1	MET+ SU	4
Kazda 2006[16]	Glargine vs lisproMix50/50	24	107	51.4	58.9	30.1	5.7	8.1	9.5	3	MET/SU/TZD/ α-Glucosidase inhibitors/Glinides	3
Strojek 2009[17] (intention-to-treat)*	Glargine vs BIAsp70/30, plus MET + SU	26	469	43.9	56	29.1	9.3	8.5	_	3.1	MET/SU	3
Buse 2009[18] (intention-to-treat)	Glargine vs lisproMix 75/25, plus previous OHA	24	2091	52.8	57	32	9.5	9.05	10.8	3.9	MET/SU/TZD	3
Raskin 2005[19] (intention-to-treat)	Glargine vs BIAspart 70/30, plus MET	28	233	54.5	52.4	31.5	9.2	9.77	13.8	3.1	MET/other agents	3
Malone 2004[20] (crossover) (intention-to-treat)	Glargine vs lisproMix75/25, plus MET	16	105	62.9	55	30.4	8.95	8.7	8.5	3.5	MET/SU/Glinides /α-Glucosidase inhibitors/TZD	4
NCT00377858[21] (intention-to-treat)	Glargine plus lispro vs lisproMix	36	479	47.6	59	29.3	11.3	9.47	_	3.9	Two or thee OHA	3
Long-acting insulin analogs vs intermediate-acting human NPH insulin												
De Mattia 2009[22] (cross-over)	Glargine vs NPH, plus previous OHAs	24	20	70	59.4	29.5	_	9.3	11.3	_	MET+SU	2
Pan 2007[23]*	Glargine vs NPH, plus SU	24	443	42.5	56.1	24.95	10.15	9.035	12.5	2.8	SU + other OHA	2
Eliaschewitz 2006[24]	Glargine vs NPH, plus SU	24	481	40.5	56.6	27.25	10.55	9.15	11.1	2.8	SU/MET/ α-Glucosidase inhibitor	2
Yki-Jarvinen 2006[25] (intention-to-treat)	Glargine vs NPH, plus MET	36	110	63.5	56.5	31.65	9	9.55	13	4	MET/SU	4

Table 1 | (*Continued*)

Author, Year, Reference	Groups	Study length (weeks)	Patients (*n*)	Men (%)	Mean age (years)	Mean BMI (kg/m^2)	Diabetes duration (years)	Start HbA_{1c} (%)	Start FPG (mmol/L)	Hypoglycemia (<mmol/L)	Previous treatment	Quality score
Philips-Tsimikas 2006 [26] (intention-to-treat)	Detemir vs NPH, plus previous OHA	20	333	56.8	58.5	30	10.3	9.04	11.1	3.1	MET/SU/TZD/ α-Glucosidase inhibitor	4
Hermansen 2006[27] (intention-to-treat)*	Detemir vs NPH, plus previous OHA	24	475	53.1	60.9	29.0	9.7	8.56	11	4	MET/SU/ α-Glucosidase inhibitor	4
Riddle 2003[28] (intention-to-treat)	Glargine vs NPH, plus previous OHA	24	756	55.5	55.5	32.35	8.7	8.59	10.9	4	SU/MET/TZD	4
Fritsche 2003[29] (intention-to-treat)	Glargine vs NPH, plus SU	28	459	53.7	61	28.7	8.8	9.1	12.1	4.2	SU/MET/ α-Glucosidase inhibitor	4
Yki-Jarvinen 2000[30] (intention-to-treat)	Glargine vs NPH, plus previous OHA	52	422	54	59	28.9	10	9	_	2.8	MET/SU/ α-Glucosidase inhibitor	4
Long-acting insulin analogs vs GLP-1 analogs												
Davies 2009[31] (intention-to-treat)	Glargine vs exenatide, plus previous OHA	26	234	68.4	56.5	34.1	8.7	8.57	10.5	3.4	MET/SU/TZD	3
Bunck 2009[32] (intention-to-treat)	Glargine vs exentide, plus MET	52	69	65.3	58.4	30.5	4.85	7.5	9.2	3.3	MET	3
Russell-Jones[33] (intention-to-treat)	Glargine vs liraglutide, plus MET + SU	26	462	58.5	57.6	30.4	9.5	8.3	9.1	3.1	MET/SU	4
Barnett 2007[34] (crossover) (intention-to-treat)	Glargine vs exenatide, plus previous OHA	16	114	47.1	54.9	31.1	7.4	8.95	12.1	3.3	MET/SU	4
Heine 2005[35] (intention-to-treat)*	Glargine vs exenatide, plus previous OHA	26	549	55.8	58.9	31.4	9.55	8.25	10.3	3.4	MET + SU	4

BMI, body mass index; GLP-1, glucagon-like peptide-1; MET, metformin; NPH, neutral protamine Hagedorn; NPL, neutral protamine Lispro; OHA, oral hypoglycemic agent; SU, sulfonylurea; TZD, thiazolidinedione.

*Standard deviation of difference between baseline and end of study was calculated according to the approach indicated in Cochrane Collaboration, 2004 (http://www.cochrane-net.org).

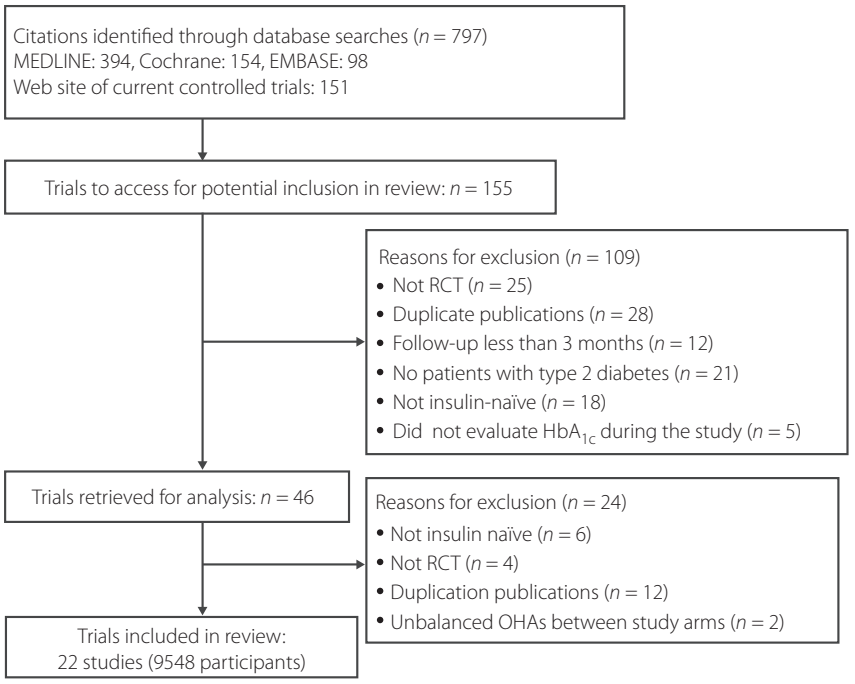

Figure 1 | Study flow diagram (*n* = number of trial reports). RCT, randomized clinical trials.

included the use of oral glucose-lowering medications in conjunction with insulin (Table 1).

Long-acting Insulin Analogs vs Rapid-acting Insulin Analogs

HbA_{1c}

Pooling studies showed that long-acting insulin analogs were not statistically significant to rapid-insulin analogs in decreasing HbA_{1c} (WMD 0.32%, 95% CI −0.02 to 0.65), but this varied between studies (I^2 = 75.3%; Figure 2a)[11,15,16]. Heterogeneity was substantially reduced when a study with shorter diabetes duration and lower baseline HbA_{1c} was removed (WMD 0.14%, 95% CI −0.02 to 0.29; I^2 = 0%)[16]. The SD for the change in one study were imputed from baseline and final SD[15].

Fasting Glucose and Postprandial Glucose

Pooling studies showed that long-acting insulin analogs were not statistically significant to rapid-acting insulin analogs in decreasing fasting glucose (WMD −1.36 mmol/L, 95% CI −3.21 to 0.49), but with high heterogeneity (I^2 = 97.2%), which was not explained by baseline HbA_{1c} levels or combination therapy of OHA or treatment targets[11,15,16]. However, long-acting insulin analogs were less effective than rapid-acting insulin analogs in decreasing morning postprandial glucose (WMD 0.78 mmol/L, 95% CI 0.38–1.19) with no heterogeneous (I^2 = 5.3%; Table 2)[11,15,16].

Weight Gain

Pooling citations showed that, compared with rapid-acting insulin analogs, long-acting insulin analogs were significantly associated with less weight gain (WMD −1.57 kg, 95% CI −3.01 to −0.13), but with heterogeneity (I^2=73.3%; Table 2)[11,15,16]. However, subgroup analysis after removing a study with longer study length and the use of detemir as the comparator did not show statistical differences between the two groups with no heterogeneity (WMD −0.77 kg, 95% CI −1.55 to 0.01; I^2 = 20.3%)[11].

Daily Insulin Dose by Bodyweight

Pooling studies showed no significant differences in daily insulin dosages between rapid-acting insulin analogs and long-acting insulin analogs (WMD −0.01 IU/kg per day, 95% CI −0.16 to 0.14), but with heterogeneity (I^2 = 59.7%; Table 2)[11,16].

Hypoglycemia

Pooling studies showed no significant difference in incidence of total hypoglycemia between long-acting and rapid-acting insulin analogs (OR 0.23, 95% CI 0.05–1.13), but with heterogeneity (I^2 = 91.2%), which was not explained by baseline HbA_{1c} levels or combination therapy of OHA or two long-acting insulin analogs (Table 2)[11,15,16]. Pooled analysis on severe hypoglycemia or nocturnal hypoglycemia was not possible as a result of insufficient data. Two citations[11,15] reported no significant differences in rates of severe hypoglycemia and one citation[15] observed no significant differences in rates of nocturnal hypoglycemia between two treatment arms.

Adverse Events

Pooling studies showed no significant difference in any adverse events between long-acting and rapid-acting insulin analogs

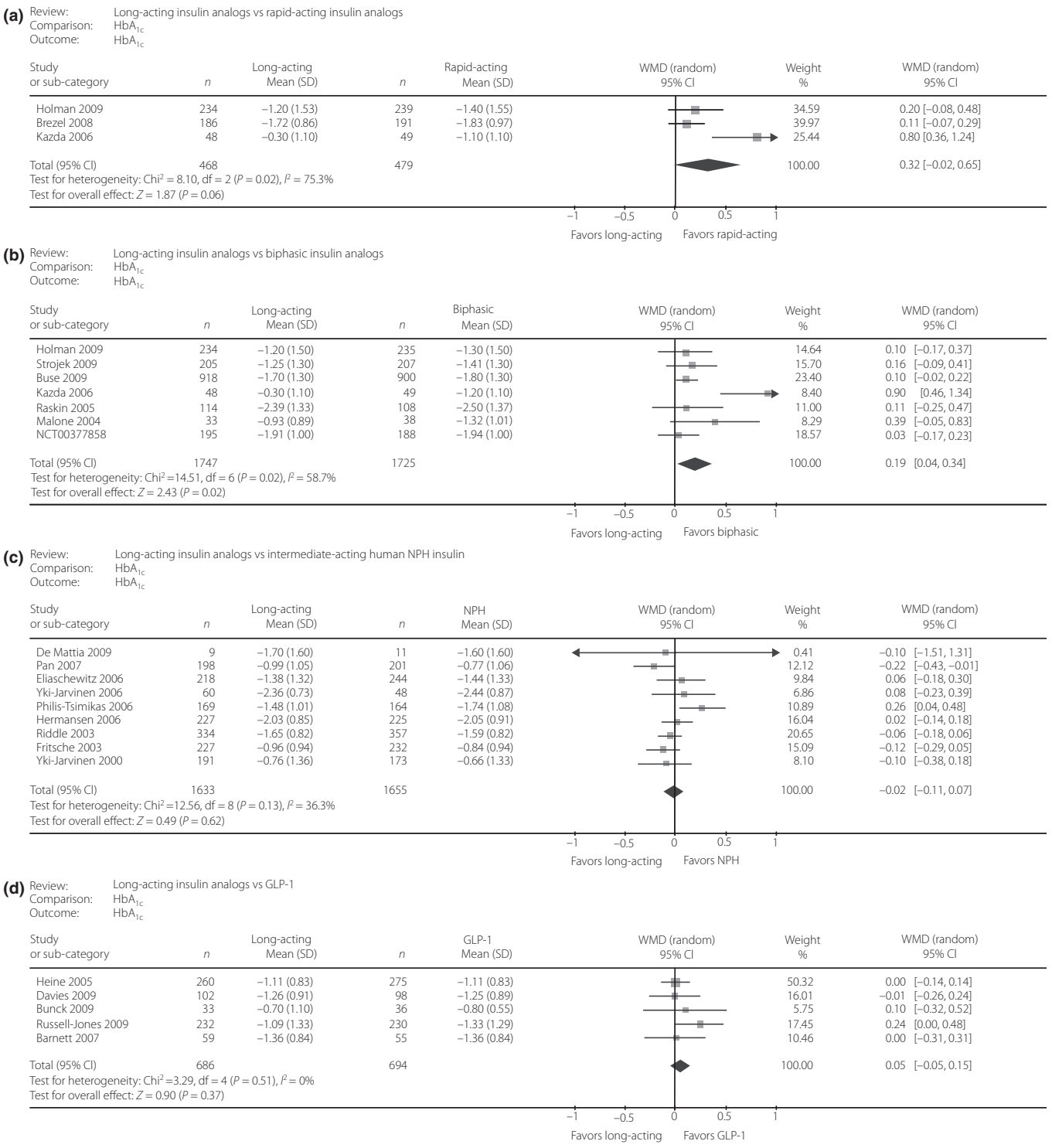

Figure 2 | (a) Long-acting insulin analogs vs rapid-acting insulin analogs. (b) Long-acting insulin analogs vs biphasic insulin analogs. (c) Long-acting insulin analogs vs intermediate-acting human neutral protamine Hagedorn (NPH) insulin. (d) Long-acting insulin analogs vs glucagon-like peptide-1 (GLP-1) analogs. WMD, weighted mean differences.

(OR 1.51, 95% CI 0.65–3.5), but with heterogeneity (I^2 = 65.6%), which was not explained by baseline HbA_{1c} levels or combination therapy of OHA, or one form of two long-acting insulin analogs (Table 2)[11,15,16]. Pooled analysis on treatment-related adverse events or withdrawal a result of adverse events was not possible because of insufficient data.

Table 2 | Pooled results for comparisons

Outcome title	No. studies	No. participants	Statistical method	Effect size	*P*-value	
					Test for heterogeneity	Test for effect I^2 (%)
Change in fasting glucose (mmol/L)						
Long-acting insulin analogs vs rapid-acting insulin analogs	3	470 vs 481	WMD (95% CI)	−1.36 (−3.21, 0.49)	0.15	97.2
Long-acting insulin analogs vs biphasic insulin analogs	4	1311 vs 1289	WMD (95% CI)	−0.57 (−1.29, 0.14)	0.11	87.2
Long-acting insulin analogs vs human NPH insulin	6	1206 vs 1246	WMD (95% CI)	−0.20 (−0.38, −0.02)	0.03	0
Long-acting insulin analogs vs GLP-1 analogs	4	468 vs 484	WMD (95% CI)	−1.35 (−1.64, −1.06)	<0.0001	0
Change in postprandial glucose (mmol/L)						
Long-acting insulin analogs vs rapid-acting insulin analogs	3	465 vs 478	WMD (95% CI)	0.78 (0.38, 1.19)	0.0001	5.3
Long-acting insulin analogs vs biphasic insulin analogs	3	398 vs 390	WMD (95% CI)	−0.52 (−1.25, 0.21)	0.17	67.3
Change in weight (kg)						
Long-acting insulin analogs vs rapid-acting insulin analogs	3	465 vs 478	WMD (95% CI)	−1.57 (−3.01. −0.13)	0.03	73.3
Long-acting insulin analogs vs biphasic insulin analogs	4	1311 vs 1289	WMD (95% CI)	−1.25 (−1.64, −0.87)	<0.0001	5.3
Long-acting insulin analogs vs human NPH insulin	6	1208 vs 1199	WMD (95% CI)	−0.32 (−1.10, 0.45)	0.41	6.3
Long-acting insulin analogs vs GLP-1 analogs	5	688 vs 696	WMD (95% CI)	4.12 (3.25, 4.99)	<0.0001	74.8
Daily insulin doses by bodyweight (U/kg)						
Long-acting insulin analogs vs rapid-acting insulin analogs	2	279 vs 287	WMD (95%CI)	−0.01 (−0.16, 0.14)	0.91	59.7
Long-acting insulin analogs vs biphasic insulin analogs	6	1646 vs 1617	WMD (95% CI)	−0.07 (−0.14, 0.00)	0.04	87.2
Long-acting insulin analogs vs human NPH insulin	5	896 vs 925	WMD (95% CI)	0.03 (0.01, 0.06)	0.01	99.3
Incidence of total hypoglycemia (%)						
Long-acting insulin analogs vs rapid-acting insulin analogs	3	465 vs 478	OR (95% CI)	0.23 (0.05, 1.13)	0.07	91.2
Long-acting insulin analogs vs biphasic insulin analogs	6	1789 vs 1759	OR (95% CI)	0.72 (0.56, 0.94)	0.01	61.2
Long-acting insulin analogs vs human NPH insulin	6	998 vs 999	OR (95% CI)	0.57 (0.45, 0.72)	<0.00001	30.3
Incidence of severe hypoglycemia (%)						
Long-acting insulin analogs vs biphasic insulin analogs	3	1265 vs 1231	OR (95% CI)	0.62 (0.31, 1.21)	0.16	0
Long-acting insulin analogs vs human NPH insulin	5	1185 vs 1235	OR (95% CI)	0.78 (0.45, 1.35)	0.37	20.8
Long-acting insulin analogs vs GLP-1 analog	3	423 vs 429	OR (95% CI)	1.55 (0.37, 6.57)	0.55	55.8
Incidence of nocturnal hypoglycemia (%)						
Long-acting insulin analogs vs biphasic insulin analogs	3	1256 vs 1237	OR (95% CI)	0.99 (0.84, 1.16)	0.89	0
Long-acting insulin analogs vs human NPH insulin	4	851 vs 878	OR (95% CI)	0.46 (0.37, 0.58)	<0.0001	0
Incidence of any adverse events (%)						
Long-acting insulin analogs vs rapid-acting insulin analogs	3	465 vs 478	OR (95% CI)	1.51 (0.65, 3.50)	0.33	65.6
Long-acting insulin analogs vs biphasic insulin analogs	3	1372 vs 1348	OR (95% CI)	0.78 (0.60, 1.02)	0.07	0
Long-acting insulin analogs vs human NPH insulin	4	648 vs 654	OR (95% CI)	0.86 (0.67, 1.11)	0.25	19.6
Long-acting insulin analogs vs GLP-1 analog	3	430 vs 436	OR (95% CI)	0.33 (0.13, 0.85)	0.02	84
Incidence of treatment related adverse events (%)						
Long-acting insulin analogs vs human NPH insulin	3	646 vs 667	OR (95% CI)	1.23 (0.82, 1.86)	0.32	6.3
Long-acting insulin analogs vs GLP-1 analog	3	430 vs 436	OR (95% CI)	0.04 (0.03, 0.06)	<0.0001	0
Withdrawal due to adverse events (%)						
Long-acting insulin analogs vs human NPH insulin	3	672 vs 701	OR (95% CI)	0.68 (0.27, 1.67)	0.39	0
Long-acting insulin analogs vs GLP-1 analog	4	460 vs 466	OR (95% CI)	0.19 (0.05, 0.66)	0.009	37.9

GLP-1, glucagon-like peptide-1; NPH, neutral protamine Hagedorn; WMD, weighted mean differences.

Long-acting Insulin Analogs vs Biphasic Insulin Analogs

HbA$_{1c}$

Pooling studies showed that long-acting insulin analogs were less effective than biphasic insulin analogs in decreasing HbA$_{1c}$ (WMD 0.19%, 95% CI 0.04–0.34; Figure 2b), but this effect varied between studies (I^2 = 58.7%)[11,16–21]. Heterogeneity was substantially reduced when a study with shorter diabetes duration and lower baseline HbA$_{1c}$ was removed (WMD 0.11%, 95% CI 0.02–0.19; I^2 = 0%)[16]. The SD for change in three studies were calculated, in which two studies were imputed from 95% CI and *P*-values for the difference in means[17,21], and the other study was imputed from the baseline and final SD[19].

Fasting Glucose and Postprandial Glucose

Pooling studies showed that long-acting insulin analogs were not statistically significant to biphasic insulin analogs in decreasing fasting glucose (WMD −0.57 mmol/L, 95% CI −1.29 to 0.14)[11,16,18,19] and morning postprandial glucose (WMD −0.52 mmol/L, 95% CI −1.25 to 0.21)[11,16,19], but with high heterogeneity (fasting glucose I^2 = 87.2%; postprandial glucose I^2 = 67.3%; Table 2). Heterogeneity in fasting glucose or postprandial glucose was not explained by baseline HbA$_{1c}$ levels or combination therapy of OHA or the treatment target. The SD for change in two studies were calculated from the baseline and final SD[18,19].

Weight Gain

Pooling citations showed that, compared with biphasic insulin analogs, long-acting insulin analogs were significantly associated with less weight gain (WMD −1.25kg, 95% CI −1.64 to −0.87), the effect was not heterogeneous (I^2 = 5.3%; Table 2)[11,16,18,19].

Daily Insulin Dose by Bodyweight

Pooling studies showed daily insulin dosages by bodyweight in long-acting insulin analogs group were lower than those in biphasic insulin analogs group (WMD −0.07 IU/kg per day, 95% CI −0.14 to 0.00), but with heterogeneity (I^2 = 87.2%; Table 2)[11,17–21].

Hypoglycemia

Pooling studies showed that long-acting insulin analogs were associated with a lower incidence of total hypoglycemia compared with biphasic insulin analogs (OR 0.72, 95% CI 0.56–0.94), but this was highly varied (I^2 = 61.2%)[11,16–19,21]. Heterogeneity was substantially reduced when a study with higher baseline HbA$_{1c}$ (9.77%) was removed (OR 0.82, 95% CI 0.71–0.94; I^2 = 0%)[19]. Pooling studies reported a non-significant difference in incidence of nocturnal hypoglycemia (OR 0.99, 95% CI 0.84–1.16)[18,20,21] and severe hypoglycemia (OR 0.62, 95% CI 0.31–1.21)[17–19] between two treatment arms, the effects were not heterogeneous for both comparisons (I^2 = 0%; Table 2).

Adverse Events

Pooling three studies showed no significant difference in incidence of any adverse events between long-acting and biphasic insulin analogs (OR 0.78, 95% CI 0.60–1.02) (Table 2)[11,17,18]. Pooled analysis on treatment-related adverse events or withdrawal as a result of adverse events was not possible because of insufficient data.

Long-acting Insulin Analogs vs Intermediate-acting Human NPH Insulin

HbA$_{1c}$

Pooling studies showed that change of HbA$_{1c}$ from baseline to study end-point was not statistically significant between two treatment arms (WMD −0.02%, 95% CI −0.11 to 0.07; Figure 2c), the effect was not heterogeneous between studies (I^2 = 36.3%)[22–30]. The SD of change in six studies were imputed from baseline and final SD[23,25,27–30].

Fasting Glucose and Postprandial Glucose

Pooling citations showed that long-acting insulin analogs were superior in decreasing fasting glucose compared with NPH insulin (WMD −0.20 mmol/L, 95% CI −0.38 to −0.02), the effect was not heterogeneous (I^2 = 0%; Table 2)[23–26,28,29]. Pooled analysis on postprandial glucose was not possible as a result of lack of data.

Weight Gain

Pooling citations showed that long-acting insulin analogs and NPH insulin have similar effects on weight gain (WMD −0.32 kg, 95% CI −1.10 to −0.45), but this varied highly (I^2 = 86.3%; Table 2)[25–30]. Heterogeneity was substantially reduced when two studies with detemir were removed (WMD 0.16 kg, 95% CI −0.25 to 0.56; I^2 = 0%)[26,27]. Furthermore, pooling these two citations with detemir showed that detemir has less weight gain than NPH (WMD −1.26 kg, 95% CI −1.70 to −0.83), but with high heterogeneity (I^2 = 60%)[26,27]. The SD for change in two studies were calculated from 95% CI and *P*-values for the difference in means[26,27].

Daily Insulin Dose by Bodyweight

Pooling studies showed daily insulin dosages by bodyweight in the long-acting insulin analogs group were higher than those in the NPH insulin group (WMD 0.03 IU/kg per day, 95% CI 0.01–0.06), but with heterogeneity (I^2 = 99.3%; Table 2)[22,24,26,28,30].

Hypoglycemia

Pooling citations showed that long-acting insulin analogs were associated with a lower incidence of total hypoglycemia (OR 0.57, 95% CI 0.45–0.72)[24–27,29] and nocturnal hypoglycemia[24,26,27,29] (OR 0.46, 95% CI 0.37–0.58) compared with NPH insulin; both the effect estimates were not heterogeneous (I^2 = 30.3% for total hypoglycemia and I^2 = 0% for nocturnal hypoglycemia). Pooling citations reported a non-significant difference in incidence of severe hypoglycemia between two arms (OR 0.78, 95% CI 0.45–1.35), the effect was not heterogeneous (I^2 = 20.8%; Table 2)[24,26–29].

Adverse Events

Pooling citations showed a non-significant difference in any adverse events (OR 0.86, 95% CI 0.67–1.11)[23–26], treatment-related adverse events (OR 1.23, 95% CI 0.82–1.86)[23,24,27] and withdrawal as a result of adverse events (OR 0.68, 95% CI 0.27–1.67)[25,27,29] between long-acting insulin analogs and NPH insulin. The effects were not heterogeneous for all these outcomes (any adverse events I^2 = 19.6%; treatment-related adverse events I^2 = 6.3%; withdrawal as a result of adverse events, I^2 = 0%; Table 2).

Long-acting Insulin Analog vs GLP-1 Analogs

HbA_{1c}

Pooling citations showed a non-significant difference in change of HbA_{1c} from baseline to study end-point between two treatment arms (WMD −0.05%, 95% CI −0.05 to 0.15), the effect was not heterogeneous (I^2 = 0%; Figure 2d)[31–35]. The SD of change in one study were imputed from 95% CI for differences in means[35].

Fasting Glucose and Postprandial Glucose

Pooling four citations showed that long-acting insulin analog was superior in decreasing fasting glucose (WMD −1.35 mmol/L, 95% CI −1.64 to −1.06) than GLP-1 analogs, the effect was not heterogeneous (I^2 = 0%; Table 2)[31,32,34,35]. Pooled analysis on postprandial glucose was not possible as a result of lack of data.

Weight Change

Pooling five citations showed that, compared with GLP-1 analogs, long-acting insulin analog was associated with greater weight gain (WMD 4.12 kg, 95% CI 3.25–4.99), but with high heterogeneity (I^2 = 74.8%; Table 2)[31–35]. Heterogeneity was reduced when a study with higher starting body mass index was removed (WMD 3.81 kg, 95% CI 3.39–4.23; I^2 = 35.5%)[31]. The SD for change in one study were calculated from 95% CI and *P*-values for the difference in means[35].

Hypoglycemia

Pooled analysis on total or nocturnal hypoglycemia was not possible as a result of different units between studies. Four studies reported no differences in the episode or incidence or event of total hypoglycemia between two treatment arms[31,33–35]. One study reported that hypoglycemia was more frequent in the glargine group (24.2 vs 8.3%, *P*-value was not shown)[33]. In addition, three citations reported GLP-1 analogs were significantly associated with a lower risk of nocturnal hypoglycemia than long-acting insulin analogs[32,33,35]. Pooling citations reported no difference in severe hypoglycemia between two treatment arms (OR 1.55, 95% CI 0.37–6.57), but with high heterogeneity (I^2 = 55.8%; Table 2)[31,34,35]. Heterogeneity was reduced (OR 0.89, 95CI 0.36–2.23; I^2 = 0%) when a study with higher duration and baseline HbA_{1c} was removed[34].

Adverse Events

Pooling citations showed that, compared with GLP-1 analogs, long-acting insulin analog was associated with less incidence of any adverse events (OR 0.33, 95% CI 0.13–0.85)[31,34,35], treatment-related adverse events (OR 0.04, 95% CI 0.03–0.06)[31,34,35], and withdrawal as a result of adverse events (OR 0.19, 95% CI 0.05–0.66)[31,32,34,35]. The effect estimates were heterogeneous for any adverse events (I^2 = 84%), but not heterogeneous for treatment-related adverse events and withdrawal as a result of adverse events (treatment-related adverse events I^2 = 0%; withdrawal as a result of adverse events I^2 = 37.9%; Table 2).

DISCUSSION

We found that all the included preparations helped to keep reducing HbA_{1c} levels by an average of 1.1–1.6% with 29–72 weeks follow up. Long-acting insulin analogs-based regimens were not statistically significant to rapid-acting insulin analogs or NPH insulin or GLP-1 analogs-based regimens in terms of decreasing HbA_{1c}. Where there were statistical differences between long-acting insulin analogs and biphasic insulin analogs-based regimens in decreasing HbA_{1c}, the differences (0.19%) were sufficiently small to have minimal if any clinical significance.

We observed that the clinical benefits of long-acting insulin analogs were associated with less weight gain over biphasic insulin analogs. The superiority in less weight gain of long-acting insulin analogs over rapid-acting insulin analogs was inconsistent as a result of heterogeneity. Pooling analysis on studies with detemir or glargine noted that detemir, but not glargine, was associated with less weight gain over NPH insulin, consistent with other reviews[36,37]. Long-acting insulin analogs were associated with greater weight gain in comparison with GLP-1 analogs.

As well, we found clinical advantages for long-acting insulin analogs over biphasic insulin analogs in the incidence of total hypoglycemia. Long-acting insulin analogs were associated with a lower incidence of total hypoglycemia and nocturnal hypoglycemia over NPH insulin.

In addition, long-acting insulin analogs were superior to GLP-1 analogs in fewer risks of any adverse events, treatment related adverse events and withdrawal as a result of adverse events. It should be stated that many of the treatment-related adverse events with GLP-1 analogs are related to gastrointestinal side-effects, notably nausea, vomiting and diarrhea. The pooled analysis on micro- and macrovascular complications was not possible, because no study evaluated these long-term outcomes.

These results are important, because the aim of early intensive treatment is glycemic control without induction of hypoglycemia or weight gain, and in the long-term, reduction in micro- and macrovascular complications. UKPDS showed that a lower 0.9% of HbA_{1c} value was associated with a reduced 25% (P = 0.0099) risk of microvascular complications and a reduced 16% (P = 0.052) risk of myocardial infarction compared with conventional therapy[38]. This suggests that reduced HbA_{1c} levels by an average of 1.1–1.6% in our analyses might well equate to

significantly reduced risks of complications. The difference between long-acting insulin analogs and biphasic insulin analogs appeared to be slight (0.19%), and the difference for subgroup analysis after removing heterogeneity was even less (0.11%). There are insufficient data to determine whether marginal reduction in HbA_{1c} is of benefit in reducing diabetes-related complications. It has, however, been reviewed by us and others[8] that biphasic insulin decreased HbA_{1c} level at the expense of an increased risk of total hypoglycemia and more weight gain. It seems likely that long-acting insulin initiation by means of one injection might facilitate patients' acceptance of insulin initiation[39].

Inconsistent with our findings to some extent, previous reviews observed that a greater reduction of 0.45% in HbA_{1c} was seen for biphasic and prandial insulin-based regimens compared with basal insulin based on regimens in type 2 diabetics failing on OHA[8]. Given the weight of the 4-T study in the meta-analysis, these findings could be partly explained by the included 3-year results, in which the superiority of the prandial and biphasic insulin relative to basal insulin at 1-year disappeared or decreased. The difference emphasizes the need to carry out long-term, high-quality studies specifically designed to determine the clinical outcomes, which are particularly important in the setting of chronic disease, such as type 2 diabetes.

The present study had limitations. The ability to understand the heterogeneity for all comparisons remains limited as a result of a small number of studies and variations in quality of studies. To address this limitation, a random-effects model was used for analysis regardless of the presence or absence of statistical heterogeneity. The small number of studies also limited our ability to fully address the potential publication bias. Furthermore, we included studies that included both crossover and parallel designs. These might be the potential sources of heterogeneity of findings. However, it did reflect the state of clinical research in this area; and consistent with our findings, previous reviews also had such methodological limitations[8,9].

In conclusion, for insulin-naïve patients with type 2 diabetes failing on oral agents, initiating long-acting insulin analogs seems likely to provide glycemic control similar to rapid-acting insulin analogs or NPH insulin or GLP-1 analogs and is marginally inferior in glycemic control compared with biphasic insulin analogs with fewer side-effects. High-quality studies are needed to evaluate the long-term effects of insulin preparations on clinical outcomes.

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