ORIGINAL RESEARCH

Efficacy and Safety of Basal Analog Regimens in Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: This study compared basal analog (BA: glargine U100/mL and detemir) and premix (PM: human, lispro and aspart biphasic) insulin regimens in terms of their efficacy and safety in type 2 diabetes mellitus patients.

Methods: Searches of MEDLINE, Embase, and CENTRAL identified primary randomized controlled trials (RCTs) $\geq$ 12 weeks in duration that compared BA or PM insulin regimens in adults with T2DM, with $\geq$ 30 patients per arm. A

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systematic literature review and a pairwise meta-analysis were performed using a random effects model adjusted for between-study variability. Analyses were conducted based on frequency of bolus insulin and PM injections, PM ratio and type, BA type, race, follow-up period, and baseline glycosylated hemoglobin (HbA1c).

Results: Twenty-two primary RCTs with 9691 patients were included. The BA and PM regimens yielded similar changes in HbA1c and postprandial glucose levels, with a statistically significant reduction in fasting glucose [mean difference (MD) $-$ 0.61 mmol/L (95% confidence interval (CI) $-$ 0.90, $-$ 0.32), I^2 = 89.6%]. The BA regimens showed significantly reduced rates of total hypoglycemia [odds ratio (OR) 0.77 (95% CI 0.64, 0.92), I^2 = 65.3%] and changes in body weight [MD $-$ 0.48 kg (95% CI $-$ 0.86, $-$ 0.11), I^2 = 75.7%] compared to PM regimens. Stratification by PM type and dosing ratio demonstrated statistically significant reductions in HbA1c favoring BA compared to human [MD $-$ 0.39% (95% CI $-$ 0.60, $-$ 0.18), I^2 = 61.8%] or 50/50-ratio [MD $-$ 0.22% (95% CI $-$ 0.40, $-$ 0.04), I^2 = 0.0%] PM regimens. Other subgroup analyses found no difference in HbA1c change between the BA and PM regimens.

Conclusion: When compared to PM regimens, BA regimens yielded similar efficacies and better safety profiles in patients with type 2 diabetes mellitus.

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INTRODUCTION

The World Health Organization estimates that 422 million adults worldwide have type 1 or 2 diabetes, with the majority afflicted with type 2 diabetes mellitus (T2DM) [1]. In OAD-treated T2DM patients with inadequate glucose control defined as glycosylated hemoglobin (HbA1c) > 7%, guidelines support the use of basal insulin as an add-on therapy [2–4]. Basal insulin analogs (BAs), including glargine (100 U/mL) and detemir, are currently more widely used than traditional neutral protamine Hagedorn (NPH) basal insulin, as BAs provide similar efficacy while reducing the risk of hypoglycemia [5]. Insulin intensification involving the combination of a BA with prandial insulin injection, also known as a basal-plus or basal-bolus (BB) regimen, is prescribed if no improvements are observed in patients treated with adequate BA [4]. Premix (PM) insulin is another common insulin prescribed worldwide, with recommendations varying by geographic location. PM insulin consists of rapid and NPH insulin components given in different ratios; this eliminates the need for patients to mix the insulin themselves while also reducing the number of injections required each day [6].

Several studies have attempted to determine whether BA or PM insulin is more efficacious in the treatment of T2DM, but results have varied significantly by study. A systematic literature review comparing insulin analogs demonstrated that more patients achieved a clinically relevant HbA1c level with biphasic or prandial insulin when compared to BA [7]. A larger systematic literature review consisting of 55 randomized controlled trials (RCTs) revealed that a higher proportion of patients achieved HbA1c < 7% (51.2%) when treated with BB regimens compared to those treated with biphasic or prandial insulin [8]. A recent systematic literature review (2016) and pairwise meta-analysis demonstrated that there was no clinically relevant difference in the HbA1c reductions achieved with BB and PM insulin [9]. Furthermore, these systematic literature reviews did not compare the full treatment journeys of patients on BA insulin regimens (from BA insulin plus OADs to a BB regimen) and those on PM insulin regimens (from PM insulin twice daily (BID) to thrice daily (TID)). Therefore, we performed a systematic literature review and pairwise meta-analysis to determine which treatment was superior and more beneficial for patients.

METHODS

Search Strategies and Database

A comprehensive literature search of MEDLINE, Embase, and the Cochrane Central Register of Control Trials (CENTRAL) was conducted, covering the period from January 1, 1997 to October 31, 2017. A standardized review protocol was used to define the eligibility criteria applied when searching for and screening references, guided by the population, intervention, comparator, outcome, timing, setting, and study design [PICO(TSS)] framework (Table S1 in the Electronic supplementary material, ESM) [10]. Inclusion criteria included primary RCTs with adult T2DM patients, an intervention group who received a BA (insulin glargine or detemir), a comparator group who received a PM insulin, a minimum follow-up period of 12 weeks, and a minimum of 30 patients per treatment arm. The studies also needed to report data on at least one efficacy outcome (HbA1c, fasting glucose, 2-h postprandial glucose, and total insulin dose) or safety outcome (body weight and hypoglycemia). Keywords used in the search strategy included *type 2 diabetes*, *basal insulin*, *glargine*, *detemir*, *premix*, *biphasic insulin AND 50/50*, *75/25*, *70/30*. The search strategy employed for each of these databases is described in more detail in Table S2a–c of the ESM. The present article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Study Selection

Study selection and screening were conducted using the web-based platform Digital Outcome Conversion (DOC) Library (version 2.0; Doctor Evidence, LLC, Santa Monica, CA, USA), according to a screening protocol based on the PICO(TSS) criteria. An assessment of the quality of the included studies was conducted by two reviewers using the Cochrane Collaborations tool for assessing the risk of bias in randomized trials [11]. This instrument is used to evaluate seven domains of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias (other bias). Data were stored and managed in Microsoft Excel. Discrepancies were resolved by an independent reviewer.

Outcome Collection

Data extraction was conducted using the DOC Data version 2.0 software platform (Doctor Evidence) and its universal electronic extraction form, based on a standardized data configuration protocol. Continuous outcomes included change from baseline (reported or calculated) in HbA1c, fasting glucose, 2-h postprandial glucose, and body weight. Data on total insulin dose at the end of follow-up were also collected. Change from baseline was calculated for selected outcomes when the study did not report this data. This was possible if the outcome was reported at the endpoint and baseline. The change was calculated by subtracting the baseline value from the endpoint value. The standard deviation (SD) in the outcome change, assuming a correlation of 0.8, was calculated based on Eq. (1) in the Cochrane Handbook [10]:

Fasting glucose and postprandial glucose data extracted included both plasma and capillary glucose values. Postprandial glucose measurements obtained 2 h after breakfast (or, for one study, after lunch) were included. In the total insulin dose analysis, a unit conversion of U or IU to U/kg to adjust for patient body weight was performed for analytical purposes. Categorical outcomes included the proportion of patients achieving HbA1c levels < 7% or ≤ 7% and total hypoglycemia by the end of follow-up. The latter was evaluated based on the author's definition and included symptomatic and asymptomatic events, measured glucose events, and self-diagnosed events. Primary efficacy outcomes were change from baseline in HbA1c and HbA1c levels < 7% or ≤ 7%. Secondary efficacy outcomes were fasting glucose, total insulin dose at the end of the study, and 2-h postprandial glucose.

Statistical Methods

A pairwise meta-analysis (MA) was performed for the outcomes of interest (i.e., HbA1c, fasting glucose, 2-h postprandial glucose, total insulin dose, body weight, and hypoglycemia). The conventional DerSimonian-Laird random-effects model was utilized. We calculated heterogeneity across studies using the Cochran Q test and the I^2 statistic. $I^2 > 50\%$ indicated significant heterogeneity [10]. All analyses were done in R 3.5.2 using the "metafor" package [12]. The comparative efficacy for each outcome was represented by the odds ratio (OR) and the associated 95% confidence interval (CI) for categorical data, or the mean difference (MD) and the associated 95% CI for continuous data. The original comparison was stratified by BA and PM insulin frequencies, including BA once daily (QD) with or without (±) OAD vs. PM insulin BID ± OAD (9 studies: [13–21]), basal-bolus insulin given once a day (BB insulin 1×)

$$\text{SD change} = \sqrt{\text{SD2 baseline} + \text{SD2 final} - (2 \times \text{Corr} \times \text{SD baseline} \times \text{SD final})}.$$

vs. PM insulin BID (3 studies: [2, 22, 23]), basal-bolus insulin given thrice a day (BB insulin 3×) vs. PM insulin BID (2 studies: [24, 25]), BB insulin 3× vs. PM insulin TID (2 studies: [26, 27]), and basal-bolus insulin given zero to thrice daily [BB insulin stepwise (0–3×)] vs. PM insulin given zero to twice a day [PM insulin stepwise (0–2×)] (6 studies: [28–33]). These original treatment comparisons are reported in Table 1. Exploratory analyses were conducted for comparisons based on PM insulin type, PM insulin ratio, BA insulin type, race, study follow-up period, and baseline HbA1c. The studies included in each of these secondary analysis comparisons are summarized in Table S3 of the ESM.

RESULTS

Search Results

The search of relevant databases identified a total of 251 studies. Following title and abstract screening, a total of 213 studies were excluded for not aligning with the prespecified PICO(TSS) criteria. Thirty-eight references were full-text screened, of which 16 did not fit the prespecified criteria for intervention (BA insulin), outcomes (change in HbA1c, fasting glucose, 2-h post-prandial glucose, and body weight, insulin dose, hypoglycemia), outcome stratification (data not reported for intervention or comparator), study design (RCTs, phase 2–4), or number of participants (≥ 30 patients per arm), and were therefore excluded. The remaining 22 studies met the PICO(TSS) criteria and were considered for data configuration and included in the meta-analysis [2, 13–33]. A PRISMA flowchart of the study selection process is presented in Fig. 1.

Study Characteristics

A summary of study characteristics is provided in Table 1. A total of 9691 patients were included in the analysis. The most common BA insulin treatments were insulin glargine 100 U/mL (19 studies: [2, 13–15, 17–24, 26–32]) and insulin aspart (11 studies: [15, 16, 18–20,

22, 23, 25, 31–33]). The patient characteristics in each trial are also reported in Table 1. Fasting plasma glucose ranged from a mean of 5.8 mmol/L (105.1 mg/dL) in insulin glargine 100U/mL + glulisine 0–2×-treated patients [31] to 14 mmol/L (252 mg/dL) in insulin aspart BID + OAD-treated patients [20]. HbA1c levels ranged from a mean of 8.07% in patients who received insulin glargine 100 U/mL + sitagliptin [15] to 11.4% in patients who received insulin glargine 100 U/mL + metformin + sulfonylurea [13].

Quality Assessment

Table S2d in the ESM presents a summary of the quality of the 22 studies. There was generally a low risk of selection bias across the studies, with some studies judged as having an unclear risk of such bias. In eight studies [13, 16, 18, 20, 25, 28, 32, 33], inadequate methods of generating the randomization sequence were reported; similarly, seven studies were judged to have an unclear risk of allocation concealment due to insufficient details [2, 13, 15, 16, 28, 32, 33]. Risk of performance bias (pertaining to the blinding of participants and personnel) and risk of detection bias (pertaining to blinding of outcome assessment) were primarily judged to be high, as most of the studies had an open-label study design. All of the studies had a low risk of attrition and reporting bias. Finally, nearly all the studies had a low risk of other sources of bias.

Primary Efficacy Outcomes (HbA1c)

The primary efficacy outcome of mean change from baseline in HbA1c was reported or calculated in all 22 trials and included in the analysis [2, 13–33]. The MD values for the overall comparisons and for each of the five primary analysis comparisons are reported in Fig. 2a. There was no statistically significant difference in HbA1c change from baseline between patients who used BA regimens and patients who used PM insulin [− 0.04% (95% CI − 0.14, 0.07)], with significant heterogeneity of effect size across the included trials ($I^2 = 77.4\%$,

Table 1 Study characteristics

Treatment comparison	Author (year)	Study population	Follow-up period	Treatment group	Treatment group population	Age	Gender	Fasting glucose	HbA1c	Insulin dose
Basal-bolus 1× vs premix BID	Riddle (2014)	588	Baseline—60 weeks	Glargine 100 U/mL QD + glulisine 1× (++ OADs)	194	Mean 53.8 (± SD 9.08)	Female—106 (56.4%)	Mean 11.0 mmol (± SD 3.9) (plasma)	Mean 9.4% (± SD 1.7)	Mean 0.11 U/kg, population n = 189, mITT
				Aspart 70/30 BID (++ OADs)	194	Mean 53.7 (± SD 10.7)	Female—109 (56.2%)	Mean 11.3 mmol (± SD 3.6) (plasma)	Mean 9.3% (± SD 1.6)	Mean 0.11 U/kg, population n = 181, mITT
Basal-bolus 1× vs premix BID	Tinahones (2014)	478	Baseline—24 weeks	Glargine 100 U/mL QD + lispro 1× (++ metformin and/or pioglitazone)	240	Mean 57.7 (± SD 9.1)	Female—142 (59.2%)	Mean 6.2 mmol (± SD 1.8) (plasma)	Mean 8.6% (± SD 0.7)	Mean 33.5 U (± SD 17.1)
				Lispro 75/25 BID (++ metformin and/or pioglitazone)	236	Mean 57.4 (± SD 9.9)	Female—120 (50.8%)	Mean 6.4 mmol (± SD 2) (plasma)	Mean 8.7% (± SD 0.8)	Mean 33.8 U (± SD 18.7)
Basal-bolus 1× vs premix BID	Vora (2015)	335	Baseline—24 weeks	Glargine 100 U/mL QD + glulisine 1× (++ metformin)	170	Mean 61.6 (± SD 8)	Female—47 (27.6%)	Mean 6.1 mmol (± SD 1.64) (plasma), population n = 170 participant	Mean 8.6% (± SD 0.9), population n = 170 participant	Mean 45 U
				Aspart 70/30 BID (++ metformin)	164	Mean 61.6 (± SD 8.9)	Female—45 (27.4%)	Mean 6.04 mmol (± SD 1.6) (plasma), population n = 165 participant	Mean 8.6% (± SD 0.9), population n = 165 participant	Mean 42 U
Basal-bolus 3× vs premix BID	Fritsche (2010)	310	Baseline—52 weeks	Glargine 100 U/mL QD + glulisine 0-3× (++ metformin)	153	Mean 60.2 (± SD 7.5)	Female—70 (45.8%)	Mean 9.9 mmol (± SD 3) (plasma)	Mean 8.62% (± SD 0.83)	Mean 52.4 IU (± SD 23.5)
				NPH 70/30 BID (++ metformin)	157	Mean 60.9 (± SD 7.8)	Female—82 (52.2%)	Mean 9.7 mmol (± SD 3.3) (plasma)	Mean 8.51% (± SD 0.86)	Mean 58.3 IU (± SD 26.7)
Basal-bolus 3× vs premix BID	Liebl (2009)	719	Baseline—26 weeks	Detemir QD + aspart 3×	537	Mean 60.3 (± SD 9.2)	Female—231 (43%)	Mean 11.21 mmol/L (± SD 3.2) (plasma)	Mean 8.52% (± SD 1.13)	N/A
				Aspart 70/30 BID	178	Mean 61.7 (± SD 9.2)	Female—66 (37%)	Mean 10.95 mmol/L (± SD 2.9) (plasma)	Mean 8.4% (± SD 1.03)	N/A

Table 1 continued

| Treatment comparison	Author (year)	Study population	Follow-up period	Treatment group	Treatment group population	Age	Gender	Fasting glucose	HbA1c	Insulin dose
Basal-bolus 3× vs premix TID	Jia (2015)	402	Baseline—24 weeks	Glargine 100 U/mL QD + lispro 3× (++ OADs)	202	Mean 58.1 (± SD 9.07)	Female—93 (46.04%)	Mean 11 mmol (± SD 3.9) (plasma)	Mean 9.8% (± SD 3.13)	Mean 0.62 U/kg (± SD 0.21)
				Lispro 50/50 BID + lispro 75/25 QD (++ OADs)	197	Mean 59.1 (± SD 9.1)	Female—95 (48.22%)	Mean 11.3 mmol (± SD 3.6) (plasma)	Mean 9.99% (± SD 2.69)	Mean 0.63 U/kg (± SD 0.2)
Basal-bolus 3× vs premix TID	Rosenstock (2008)	374	Baseline—24 weeks	Glargine 100 U/mL QD + lispro 3× (++ OADs)	187	Mean 54 (± SD 9.2)	Female—89 (48%)	Mean 10.08 mmol (± SD 3.32) (plasma)	Mean 8.89% (± SD 1.09)	Mean 0.56 U/kg (± SD 0.27)
				Lispro 50/50 TID (++ OADs)	187	Mean 55.4 (± SD 9.8)	Female—88 (47%)	Mean 9.54 mmol/L (± SD 3.32) (plasma)	Mean 8.83% (± SD 1.04)	Mean 0.53 U/kg (± SD 0.21)
Basal-bolus stepwise vs premix stepwise	Bowering (2012)	426	Baseline—48 weeks	Glargine 100 U/mL QD + lispro 1-3× (++ metformin)	212	Mean 56.29 (± SD 9.35)	Female—107 (50.5%)	NA	Mean 9.03% (± SD 1.05)	Mean 10 U
				Lispro 75/25 1-3× (++ metformin ± sulfonylurea)	211	Mean 56.68 (± SD 8.03)	Female—118 (55.9%)	NA	Mean 8.98% (± SD 1.04)	Mean 10 U
Basal-bolus stepwise vs premix stepwise	Giugliano (2014)	344	Baseline—48 weeks	Glargine 100 U/mL QD + lispro 1-3× (++ OADs)	173	Mean 54.2 (± SD 8.6)	Female—92 (53%)	Mean 9.6 mmol/L (± SD 2.2) (plasma)	Mean 9.07% (± SD 0.99)	NA
				Lispro 75/25 or lispro 50/50 1-3× (++ OADs)	171	Mean 54.3 (± SD 8.9)	Female—84 (49%)	Mean 9.4 mmol/L (± SD 2.2) (plasma)	Mean 8.98% (± SD 0.95)	NA
Basal-bolus stepwise vs premix stepwise	Jain (2010)	484	Baseline—36 weeks	Glargine 100 U/mL QD + lispro ≤ 3× (++ OADs)	195	Mean 59.9 (± SD 9.6)	Female—94 (48.2%)	Mean 9.6 mmol/L (± SD 12.57, SE 0.9) (blood)	Mean 9.3% (± SD 1.2)	NA
				Lispro 50/50 1-3× (++ OADs)	188	Mean 58.9 (± SD 8.8)	Female—102 (54.3%)	Mean 10.2 mmol/L (± SD 12.34, SE 0.9) (blood)	Mean 9.5% (± SD 1.2)	NA
Basal-bolus stepwise vs premix stepwise	Jin (2016)	161	Baseline—24 weeks	Glargine 100 U/mL QD + glulisine 0-2×	78	Mean 59.45 (± SD 10.03)	Female—39 (50%)	Mean 105.1 mg/dL (5.83 mmol/L) (± SD 20.26) (plasma)	Mean 8.48% (± SD 0.74)	Mean 35.53 U (± SD 13.32)
				Aspart 70/30 BID	82	Mean 59.5 (± SD 8.72)	Female—43 (52.44%)	Mean 107.82 mg/dL (5.98 mmol/L) (± SD 22.84) (plasma)	Mean 8.31% (± SD 0.74)	Mean 12.49 U (± SD 2.97)

Table 1 continued

Treatment comparison	Author (year)	Study population	Follow-up period	Treatment group	Treatment group population	Age	Gender	Fasting glucose	HbA1c	Insulin dose
Basal-bolus stepwise vs premix stepwise	Linjawi (2017)	335	Baseline—32 weeks	Glargine 100 U/mL QD + insulin aspart (++ metformin + sulfonylurea)	167	Mean 56.6 (± SD 10.4)	Female—90 (53.9%)	Mean 9.6 mmol/L (± SD 2.3) (plasma)	Mean 8.2% (± SD 0.7)	Mean 0.127 U/kg
				Aspart 70/30 QD-TID (++ metformin + sulfonylurea)	168	Mean 56.6 (± SD 10.4)	Female—79 (47%)	Mean 9.7 mmol/L (± SD 2.7) (plasma)	Mean 8.3% (± SD 0.7)	Mean 0.157 U/kg
Basal-bolus stepwise vs premix stepwise	Malek (2015)	403	Baseline—50 weeks	Detemir QD + metformin (++ aspart 1–3×)	200	Mean 59.45 (± SD 10.03)	Female—113 (56.5%)	Mean 9.52 mmol/L (plasma)	Mean 8.7% (± SD 1.1)	Mean 0.1 U/kg (± SD 13.32)
				Aspart 70/30 QD-TID + metformin	203	Mean 52.6 (± SD 10.1)	Female—128 (63.1%)	Mean 10.07 mmol/L (plasma)	Mean 8.6% (± SD 1)	Mean 0.1 U/kg (± SD 2.97)
Basal ± OAD vs premix BID ± OAD	Al-Shaikh (2006)	221	Baseline—6 months	Glargine 100 U/mL QD (++ metformin + sulfonylurea)	111	NA	NA	NA	Mean 11.4% (range 8–16.4)	NA
				NPH 70/30 BID	110	NA	NA	NA	Mean 11.2	NA
Basal ± OAD vs premix BID ± OAD	Buse (2009)	2091	Baseline—24 weeks	Glargine 100 U/mL QD (++ OADs)	1046	Mean 57 (± SD 10)	Female—494 (47.2%)	Mean 10.9 mmol/L (± SD 3.1) (plasma)	Mean 9% (± SD 1.2)	NA
				Lispro 75/25 BID (++ OADs)	1045	Mean 57 (± SD 10.0)	Female—493 (47.2%)	Mean 10.7 mmol/L (± SD 3) (plasma)	Mean 9.1% (± SD 1.3)	NA
Basal ± OAD vs premix BID ± OAD	Cao (2017)	72	Baseline—16 weeks	Glargine 100 U/mL QD + sitagliptin	33	Mean 52.1 (± SD 9.6)	Female—15 (46.6%)	Mean 9.11 mmol/L (± SD 2.43) (plasma)	Mean 8.07% (± SD 0.91)	NA
				Aspart 70/30 BID	32	Mean 49.8 (± SD 11.2)	Female—16 (49.8%)	Mean 10.12 mmol/L (± SD 2.13) (plasma)	Mean 8.23% (± SD 0.81)	NA
Basal ± OAD vs premix BID ± OAD	Holman (2009)	708	Baseline—3 years	Detemir QD	234	N/A	N/A	N/A	Mean 8.5% (95% CI 8.4–8.62)	Mean 0.173 U/kg (95% CI 0.156–0.191)
				Aspart 70/30 BID	235	N/A	N/A	N/A	Mean 8.6% (95% CI 8.49–8.7)	Mean 0.182 U/kg (95% CI 0.165–0.208)

Table 1 continued

Treatment comparison	Author (year)	Study population	Follow-up period	Treatment group	Treatment group population	Age	Gender	Fasting glucose	HbA1c	Insulin dose
Basal ± OAD vs premix BID ± OAD	Janka (2005)	364	Baseline—24 weeks	Glargine 100 U/mL QD + glimepiride (++ metformin)	177	Mean 60.9 years (± SD 8.7)	Female—69 (39%)	Mean 9.5 mmol/L (± SD 1.9) (blood)	Mean 8.85% (± SD 0.98)	Mean 9.9 U (± SD 2.6)
				Human premixed 70/30 BID	187	Mean 60.4 years (± SD 9.1)	Female—80 (43%)	Mean 9.6 mmol/L (± SD 2.1) (blood)	Mean 8.83% (± SD 0.87)	Mean 20.6 U
Basal ± OAD vs premix BID ± OAD	Kann (2006)	258	Baseline—26 weeks	Glargine 100 U/mL QD + glimepiride	127	Mean 61 years (± SD 8.9)	Female—65 (51.2%)	N/A	Mean 8.9% (± SD 1.3)	Mean 0.2 U/kg
				Aspart 70/30 BID + metformin	128	Mean 61.5 years (± SD 9.3)	Female—59 (46.1%)	N/A	Mean 9.21% (± SD 1.4)	Mean 0.2 U/kg
Basal ± OAD vs premix BID ± OAD	Ligthelm (2011)	280	Baseline—24 weeks	Glargine 100 U/mL QD + glimepiride (++ metformin + insulin secretagogues ± thiazolidinedione)	143	Mean 53.5 years (± SD 10.6)	Female—59 (41.3%)	Mean 174.6 mg/dL (9.69 mmol/L) (± SD 60) (plasma), population, $n = 127$, ITT	Mean 9% (± SD 1.2)	Mean 0.39 U/kg (± SD 0.22), population, $n = 141$, safety
				Aspart 70/30 BID (++ metformin ± thiazolidinedione)	137	Mean 51.9 years (± SD 10.2)	Female—62 (45.3%)	Mean 179.7 mg/dL (9.97 mmol/L) (± SD 67.7) (plasma), population, $n = 132$, ITT	Mean 9% (± SD 1)	Mean 0.46 U/kg (± SD 0.23), population, $n = 138$, safety
Basal ± OAD vs premix BID ± OAD	Raskin (2005)	233	Baseline—28 weeks	Glargine 100 U/mL QD (++ metformin ± thiazolidinedione ± pioglitazone)	116	Mean 52.3 years (± SD 9.8)	Female—51 (44%)	Mean 243 mg/dL (13.49 mmol/L) (± SD 68.8) (plasma)	Mean 9.8% (± SD 1.4)	Mean 0.13 U/kg (± SD 0.03)
				Aspart 70/30 BID (++ metformin ± thiazolidinedione ± pioglitazone)	117	Mean 52.6 years (± SD 10.6)	Female—55 (47%)	Mean 252 mg/dL (13.99 mmol/L) (± SD 67.4) (plasma)	Mean 9.7% (± SD 1.5)	Mean 0.14 U/kg (± SD 0.03)
Basal ± OAD vs premix BID ± OAD	Zhou (2015)	105	Baseline—12 weeks	Glargine 100 U/mL QD + gliclazide	52	Mean 55.54 years (± SD 5.88)	Female—24 (46.15%)	Mean 10.49 mmol/L (± SD 2.01) (plasma)	Mean 8.48% (± SD 0.69)	Mean 0.19 U/kg (± SD 0.02)
				Human insulin 70/30 BID	53	Mean (54.39 yr) (± SD 6.86)	Female—27 (50.94%)	Mean 10.16 mmol/L (± SD 2.17) (plasma)	Mean 8.55% (± SD 0.79)	Mean 0.41 U/kg (± SD 0.1)

++ Background therapy + concurrent/concomitant, ± part of the population received but the rest did not receive the additional intervention, QD once-daily, BID twice daily, TID three times daily, OAD/OADs oral antidiabetic drugs, CI confidence interval, SD standard deviation, SE standard error, CI confidence interval, ITT intent-to-treat, mITT modified intent-to-treat
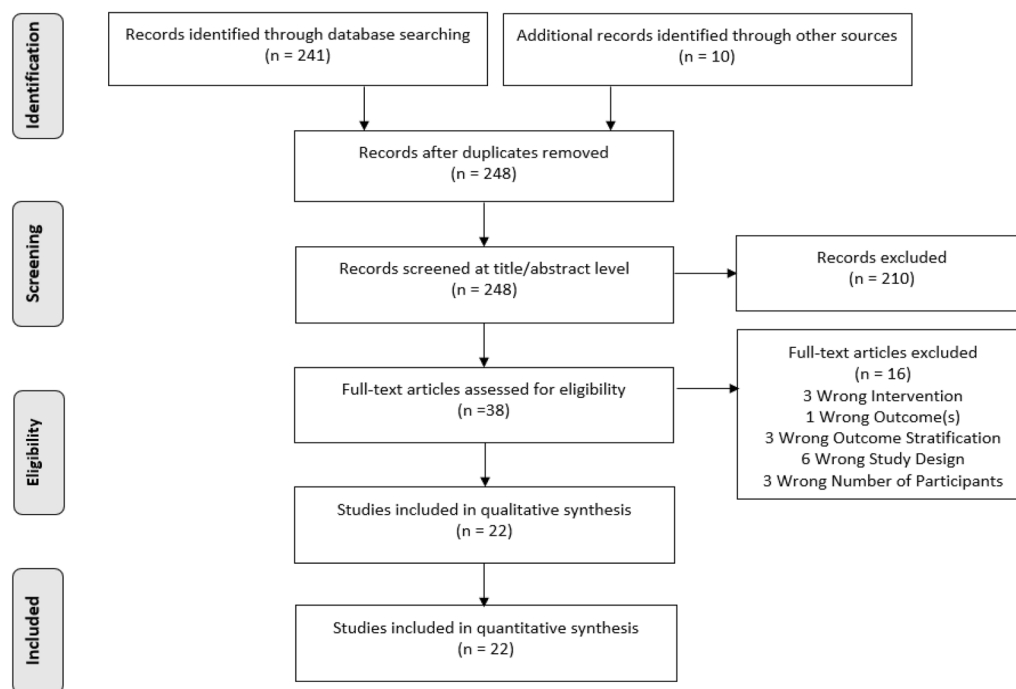
**Fig. 1** PRISMA flow diagram for the study selection process

p value < 0.05) (Fig. 2a). A comparison of BB insulin 3× to PM insulin BID highlighted a statistically significant difference in HbA1c reduction [− 0.37% (95% CI − 0.64, − 0.10)] (Fig. 2a). In contrast, BA therapy ± OAD led to a similar HbA1c change to that achieved with PM insulin in combination or without OAD [0.00% (95% CI − 0.21, 0.20)], suggesting that the change observed in the BB insulin 3× group resulted from the bolus injections (Fig. 2a). Exploratory analyses were conducted for comparisons based on BA or PM insulin types and patient/trial characteristics, as further summarized in Table S3 of the ESM. When examining PM insulin stratified by type, there was a statistically significant difference in HbA1c reduction between patients on BA insulin regimens and those receiving regular human PM insulin [− 0.39% (95% CI − 0.60, − 0.18)] (Table S4 in the ESM). A secondary analysis of PM insulin ratio also revealed a statistically significant difference in the change in HbA1c between those receiving BA insulin regimens and those receiving PM 50/50 insulin [− 0.22% (95% CI − 0.40, − 0.04)] (Table S4 in the ESM). None of the other secondary analysis comparisons showed statistically significant differences in change from baseline HbA1c (Table S4 in the ESM).

HbA1c ≤ 7% was reported and analyzed in all 22 trials [2, 13–33]. ORs for the overall comparisons and for each of the five primary analysis comparisons are reported in Fig. 2b. Overall, although there were no statistically significant differences between patients who used BA insulin regimens and those who used PM insulin [1.14 (95% CI 0.94, 1.40)], there was significant heterogeneity of effect size across the included trials ($I^2 = 78.7\%$, p value < 0.05) (Fig. 2b). The odds of achieving HbA1c ≤ 7% were highest with BB insulin 3× compared to PM insulin BID [1.76 (95% CI 1.17, 2.64)] (Fig. 2b).

Secondary Efficacy Outcomes (Fasting Glucose, 2-h Postprandial Glucose, and Insulin Dose)

Change from baseline in fasting glucose was an average of 0.61 mmol/L smaller in patients who used BA than in patients who used PM insulin regimens [− 0.61 mmol/L (95% CI − 0.90, − 0.32)] (Table 2). Three primary analyses showed statistically significant differences,
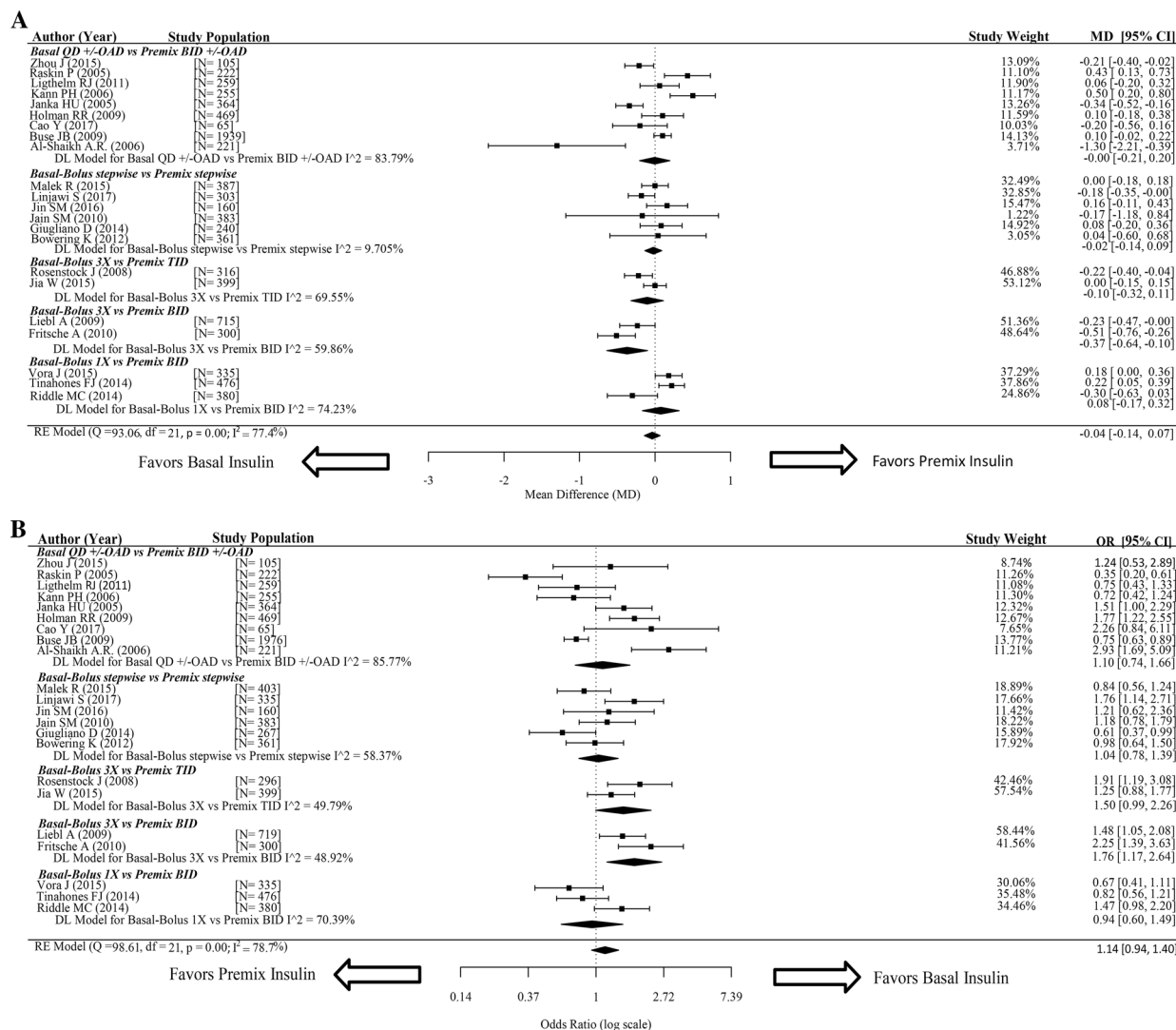
Fig. 2 Efficacy analysis for primary comparisons. The figure depicts Forest plots for pairwise meta-analysis of efficacy outcomes for **a** change from baseline HbA1c and **b** HbA1c < 7%. The I^2 value was used to assess heterogeneity. Results are shown as the mean difference (MD) for continuous data along with the associated 95% CI for change from baseline HbA1c, and the odds ratio (OR) along with the associated 95% confidence interval (CI) for HbA1c < 7%. *QD* once daily, *BID* twice daily, *TID* three times daily, *OAD/OADs* oral antidiabetic drugs, *MD* mean difference, *OR* odds ratio, *CI* confidence interval

including BB insulin stepwise versus PM insulin stepwise [− 0.99 mmol/L (95% CI − 1.42, − 0.55)], BB insulin 3× versus PM insulin TID [− 0.74 mmol/L (95% CI − 1.46, − 0.02)], and BA insulin QD ± OAD versus PM insulin BID ± OAD [− 0.59 mmol/L, 95% CI − 1.06, − 0.12)] (Table 2).

Although not statistically significant, the evidence suggests that total insulin dose was on average 0.06 U/kg lower in patients who used

BA compared to those who used PM insulin [− 0.06 U/kg (95% CI − 0.13, 0.01)] (Table 2). A significant decrease in total insulin dose was reported for the BA insulin QD ± OAD patients compared to the PM insulin BID ± OAD patients [− 0.107 U/kg (95% CI − 0.32, − 0.01)] (Table 2).

An increase from baseline in 2-h postprandial glucose was observed in patients who used BA insulin regimens compared to patients who

Table 2 Secondary efficacy outcomes: analyses of change from baseline in fasting glucose, change from baseline in 2-h postprandial glucose, and total insulin dose at end of follow-up

Mean difference (MD)	Number of studies	I^2 (%)	Estimate	95% CI	
				Lower	Upper
Fasting glucose (mmol/L)					
Overall	16	89.6	− 0.61	− 0.90	− 0.32*
Basal QD ± OAD vs premix BID ± OAD	7	83.0	− 0.59	− 1.06	− 0.12*
Basal-bolus stepwise vs premix stepwise	3	50.8	− 0.99	− 1.42	− 0.55*
Basal-bolus 3× vs premix TID	2	85.5	− 0.74	− 1.46	− 0.02*
Basal-bolus 3× vs premix BID	2	78.4	− 0.24	− 1.22	0.75
Basal-bolus 1× vs premix BID	2	66.9	− 0.51	− 1.35	0.32
Overall	17	94.2	− 0.06	− 0.13	0.01
Total insulin dose (U/kg)					
Basal QD ± OAD vs premix BID ± OAD	6	97.1	− 0.17	− 0.32	− 0.01*
Basal-bolus stepwise vs premix stepwise	5	0.0	0.00	− 0.04	0.05
Basal-bolus 3× vs premix TID	2	86.63	0.10	− 0.08	0.27
Basal-bolus 3× vs premix BID	1	0.0	0.05	− 0.07	0.17
Basal-bolus 1× vs premix BID	3	83.2	− 0.07	− 0.17	0.04
Overall	12	90.6	0.09	− 0.31	0.49
2-h postprandial glucose (mmol/L)					
Basal QD ± OAD vs premix BID ± OAD	4	81.6	0.44	− 0.11	0.99
Basal-bolus stepwise vs premix stepwise	4	87.5	0.08	− 0.83	1.00
Basal-bolus 3× vs premix TID	2	97.8	− 0.53	− 2.57	1.51
Basal-bolus 3× vs premix BID	1	0.0	− 0.60	− 1.20	0.00
Basal-bolus 1× vs premix BID	1	0.0	0.54	0.09	0.99

QD once daily, *BID* twice daily, *TID* three times daily, *OAD/OADs* oral antidiabetic drugs, *MD* mean difference, *CI* confidence interval

*p value < 0.05

used PM insulin, but this was not statistically significant [0.09 mmol/L (95% CI − 0.31, 0.49)] (Table 2).

Safety Outcomes (Hypoglycemia and Body Weight)

Total hypoglycemia was suitable for analysis in 19 trials [2, 14–27, 29–31, 33]. Results for overall comparisons and each of the five primary analysis comparisons are reported in Fig. 3a. Patients who used BA insulin regimens had a statistically significantly reduced likelihood of total hypoglycemia compared to those who used PM insulin regimens [0.77 (95% CI 0.64, 0.92)], with significant heterogeneity of effect size across the included trials ($I^2 = 65.3\%$, p value < 0.05) (Fig. 3a). The only statistically significant difference in hypoglycemia
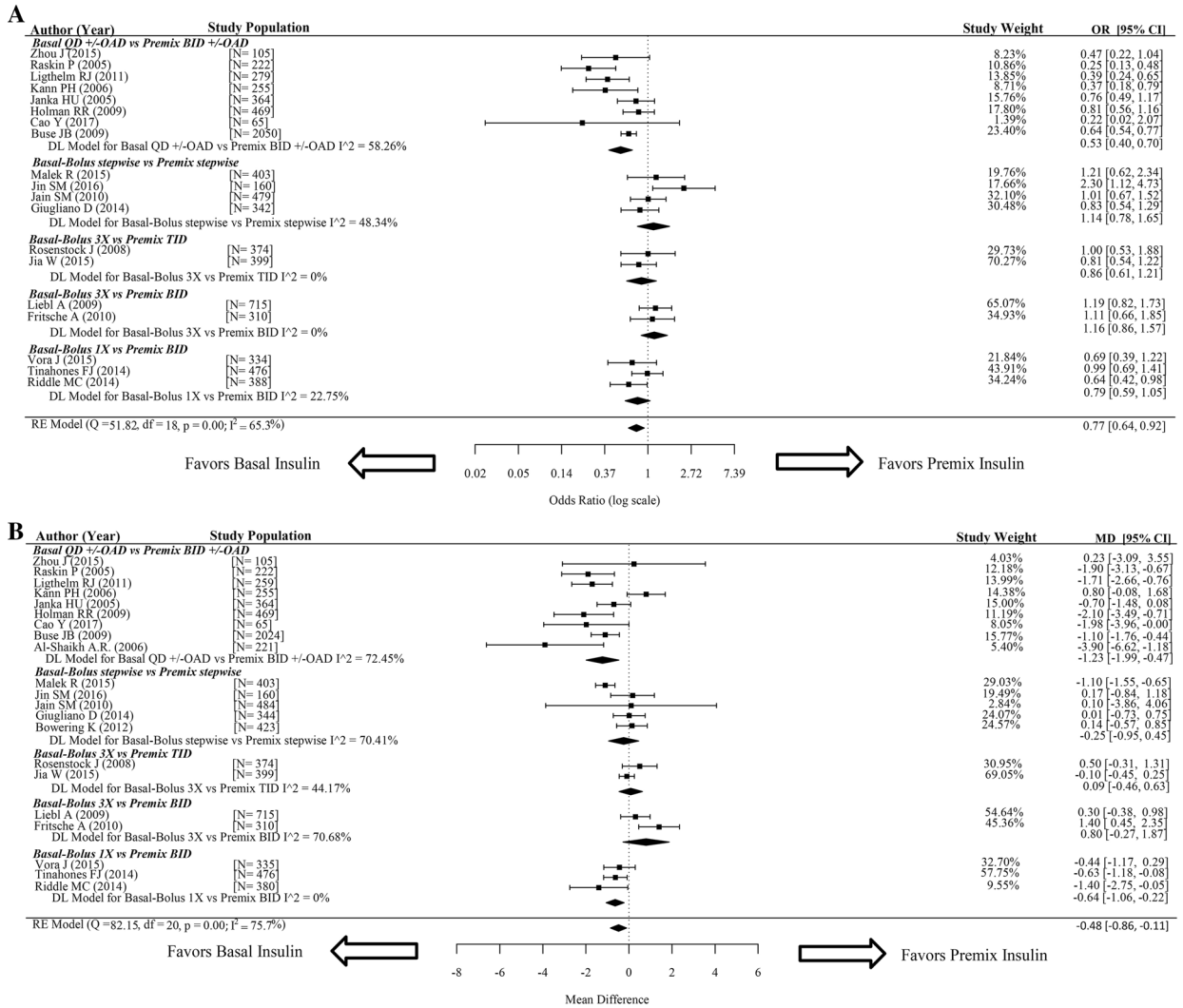
Fig. 3 Safety, primary analyses. The figure depicts Forest plots for pairwise meta-analysis of safety outcomes for **a** total hypoglycemia and **b** change from baseline in body weight. The I^2 value was used to assess heterogeneity. Results are shown as the mean difference (MD) for continuous data along with the associated 95% CI for body weight, and the odds ratio (OR) with the associated 95% confidence interval (CI) for total hypoglycemia. *QD* once daily, *BID* twice daily, *TID* three times daily, *OAD/OADs* oral antidiabetic drugs, *MD* mean difference, *CI* confidence interval

incidence in a primary comparison was between the BA insulin QD ± OAD and PM insulin BID ± OAD groups [0.53 (95% CI 0.40, 0.70)] (Fig. 3a). Other primary comparisons showed no statistical significant difference in hypoglycemia incidence (Fig. 3a). The results of exploratory analyses of total hypoglycemia for comparisons based on BA or PM insulin types and patient/trial characteristics are summarized in Table S5 in the ESM.

Mean change from baseline in body weight was suitable for analysis in 21 trials [2, 13–31, 33], with MDs for overall comparisons and each of the five primary analysis comparisons reported in Fig. 3b. There was a statistically significant difference in body weight between patients who used BA insulin regimens and patients who used PM insulin [− 0.48 kg (95% CI − 0.86, − 0.11)], with significant heterogeneity of effect size across the

included trials ($I^2 = 75.7\%$, p value < 0.05) (Fig. 3b). The comparison of the BA QD $\pm$ OAD and PM insulin BID $\pm$ OAD groups showed a significant difference in body weight change [$- 1.23$ kg (95% CI $- 1.99$, $- 0.47$)] (Fig. 3b). Body weight change was also significantly different for BB insulin 1$\times$-treated patients and PM insulin BID-treated patients [$- 0.64$ kg (95% CI $- 1.06$, $- 0.22$)] (Fig. 3b).

DISCUSSION

To the authors' best knowledge, this is the sole systematic literature review and pairwise meta-analysis from the last 5 years that compares BA and PM insulin regimens in terms of relative efficacy and safety. The evidence demonstrated a significant improvement in the efficacy outcome change from baseline in fasting glucose as well as reductions in the safety outcomes change from baseline in body weight and total hypoglycemia likelihood for BA insulin compared to PM insulin. A systematic literature review and pairwise meta-analysis demonstrated that a BA insulin regimen is the optimal choice for patients with type 2 diabetes.

To determine which specific BA or PM insulin regimen is most favorable, primary analyses were conducted based on the original frequencies of BA and PM insulin. When comparing different initial insulin regimes, BA insulin $\pm$ OAD therapy was observed to yield the most statistically significant improvements in both efficacy and safety outcomes when compared to PM insulin BID $\pm$ OAD, indicating that BA insulin may be the best choice when initiating insulin therapy in T2DM patients. During insulin therapy escalation, BB insulin 1$\times$ did not produce a statistically significant difference in efficacy compared to PM insulin BID, but it did lead to a significant decrease in body weight change. In contrast, BB insulin 3$\times$ therapy produced a statistically significant decrease in HbA1c change and an increased likelihood of achieving HbA1c $\leq 7\%$ but no statistically significant difference in change from baseline in body weight or likelihood of total hypoglycemia as compared to PM insulin BID. This demonstrates that, despite its complicated injection schedule, BB insulin 3$\times$ would be a more favorable escalation choice for patients with uncontrolled glycemia than the simpler PM insulin BID regimen.

A unique aspect of our systematic literature review and meta-analysis is that we also explored how treatment type and patient characteristics affected the change in HbA1c from baseline and total hypoglycemia. Firstly, when stratified by PM insulin type, BA insulin demonstrated statistically significant improvements in change from baseline HbA1c as compared to regular human PM and a PM ratio of 50/50 (see Table S4 of the ESM). Secondly, BA insulin yielded a statistically significant decrease in the likelihood of total hypoglycemia compared to lispro PM insulin and PM insulin with a ratio of 70/30. Lastly, our analyses revealed that the decrease in total hypoglycemia for BA as compared to PM insulin was significant in non-Asian populations, studies with a follow-up period of < 26 weeks, as well as patients with a baseline HbA1c of $\geq 9\%$ (Table S5 in the ESM). No other statistically significant difference was found in these exploratory analyses.

Although this pairwise meta-analysis provides evidence that can be used to address a question that was previously unresolved, there are limitations to this systematic literature review. The pairwise meta-analysis was conducted with a limited number of studies since only those that compared BA insulin directly to PM insulin were considered. Due to the limited number of studies included in the quantitative analysis, full evaluations of the differences in efficacy and safety between BA and PM insulin were difficult to assess. Heterogeneity was significantly (p value < 0.05) high ($> 70\%$) in most of the overall analyses due to variations in sample size and effect size. Eight additional subgroup analyses observed high levels of heterogeneity (I^2 values $> 70\%$). Exploratory analyses of PM insulin type, PM insulin ratio, BA insulin type, and ethnicity/race were limited by the number of studies included in each comparison. In addition, there was also a bias due to the overrepresentation of certain categories such as BA insulin type.

Previous systematic literature reviews and meta-analyses provided inconsistent results regarding the superiority of BA or PM insulin [7, 8]. A more recent systematic literature review claimed that there was no clinically relevant difference in efficacy and safety outcomes between BB and PM insulin [9]. Our systematic literature review differed in that it included a wider pool of studies, which permitted an exploration of not only the difference between BB and PM insulin but also between BA and PM insulin regimens ± OAD therapy. Two studies included in the 2016 systematic literature review were excluded from this systematic literature review because they were classified as a pragmatic trial [34] or a substudy [35] instead of a primary RCT. The discussed results could also have been impacted by the range of insulin treatments we considered, and thus the greater number of references that were analyzed.

CONCLUSION

In conclusion, this systematic literature review and meta-analysis revealed that BA insulin regimens yielded significant improvements in fasting glucose, body weight change, and risk of total hypoglycemia as compared to PM insulin regimens, but further research is needed to confirm these results.

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