JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Efficacy and safety of premixed versus basal-bolus regimens as intensification of insulin therapy in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized clinical trials

Mohsen Dehghani[1], Masoumeh Sadeghi[1,2], Farzaneh Barzkar[3], Mohammad Ebrahim Khamseh[3], Ashkan Torshizian[2]*, Hamid Reza Baradaran[4,5]*

[1]Department of Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran, [2]Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [3]Endocrinology Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran, [4]Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran, and [5]Ageing Clinical and Experimental Research Team, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, UK

Keywords
Basal-bolus Insulin, Premixed Insulin, Type 2 Diabetes Mellitus

***Correspondence**
Hamid Reza Baradaran
Tel.: +98 9122979926 Fax: +98 21 86701
E-mail address: baradaran.hr@iums.ac.ir, baradaran98@gmail.com, hamid.baradaran@abdn.ac.uk

Ashkan Torshizian
Tel.: +98 9151241464 Fax: +98 51 3882 7051
E-mail address: ashkan1374@gmail.com

J Diabetes Investig 2025; 16: 827–841

doi: 10.1111/jdi.70002

ABSTRACT

Aim: To estimate the efficacy and safety of the basal-bolus and premixed insulin as intensification regimens in patients with type 2 diabetes mellitus (T2DM).

Methods: A comprehensive search of online databases was performed until December 2022 to identify randomized controlled trials (RCTs) comparing premixed insulin versus basal-bolus regimen with treat-to-target intention. The Cochrane ROB-2 tool and GRADE approach were used for quality assessment and certainty of the evidence, respectively. Pooled weighted mean difference (WMD) and odds ratio (OR) were calculated using random-effects meta-analysis models.

Results: Eighteen RCTs were included in the meta-analysis, and 66% had a low risk of bias. We found no significant difference between the two regimens regarding HbA1c reduction (WMD: 0.03% [–0.05%, 0.10%]). The basal-bolus regimen improved fasting plasma glucose (FPG) more than the premixed regimen (WMD: 6.35 mg/dL [0.31, 12.39]). Both had similar effects on weight gain. The odds of developing overall, nocturnal, and severe hypoglycemia were comparable (pooled OR: 0.9, 1.02, and 1.00, respectively) with no heterogeneity. Findings of the model were robust. The certainty of the evidence was moderate to high for all outcomes except FPG.

Conclusions: Two regimens are clinically comparable. Patient preference should be considered when adopting an individualized approach in a real-world setting.

INTRODUCTION

Diabetes mellitus is a chronic and progressive metabolic disorder that affects 9.3% (463 million people) worldwide. Type-2 diabetes, which accounts for 90–95% of all cases, is caused by progressive insulin resistance and relative insulin deficiency[1]. Type 2 diabetes is initially treated with diet and oral antidiabetic drugs[2,3]. Many patients eventually require and benefit from insulin therapy due to the progressive and gradual loss of the mass of insulin-producing cells in the pancreas over 5–10 years from the onset of type-2 diabetes[4]. The goal is to achieve adequate glycemic control, which can prevent long-term complications associated with diabetes and premature death from diabetes.

Achieving this goal remains difficult in a large proportion of people with T2DM despite growing treatment options[3,5]. Initially, when insulin is prescribed, providing basic or basal

Received 28 November 2024; revised 29 December 2024; accepted 22 January 2025

insulin will be sufficient for adequate glycemic control. However, patients will gradually require additional bolus insulin injections[6]. Suppose basal insulin alone does not result in adequate glycemic control. In that case, bolus insulin can be given either as a complete basal-bolus regimen (basal insulin plus bolus insulin administered at all meals) or as a stepwise regimen, that is, starting with the most essential meal (basal plus) and then, if necessary, adding other meals to reach the full basal-bolus[7–9]. The patient can switch treatment from receiving basal insulin to premixed insulin, which is initially prescribed twice a day, and if necessary, increases to three injections a day[10,11]. The choice to intensify the treatment will depend on the clinical conditions and patient preferences[11,12]. Therefore, basal-bolus and premixed insulin regimens are the two main options for intensification of insulin therapy in people with T2DM who are not at the desired HbA1c target with previous treatment. Many studies have compared bolus and premixed insulin regimens regarding glycemic control, weight gain, and hypoglycemia; however, their results are inconsistent[13–18]. The randomized clinical trials conducted so far vary in terms of the study population, sample size, baseline body mass index, duration of diabetes, and treatment duration, which may contribute to the discrepancies in their findings. Since the clinicians face challenges in the decision to choose between basal-bolus (full basal-bolus) vs. premixed insulin (three times a day) for intensification of insulin therapy, we conducted a systematic review and meta-analysis of randomized controlled clinical trials (RCTs) to summarize and synthesize the evidence to support decision-making and to determine potential sources of inconsistency and heterogeneity across the available studies.

MATERIALS AND METHODS

The PRISMA guideline was followed for reporting the present systematic review and meta-analysis[19].

Search strategy

A comprehensive search of online databases including MEDLINE, Embase, Cochrane library ISI, Scopus, and Google Scholar was performed through December 2022 using the medical subject headings terms "premixed" or "lispro mix" or "aspart mix" or "biphasic human insulin" or "Humalog mix" or "Novolog Mix" "insulin degludec/insulin aspart" or "basal" or "long-acting insulin" or "basal-bolus insulin" or "basal plus insulin" AND "efficacy" or "safety" or "glycemic" or "glycated hemoglobin" or "fasting plasma glucose" or "fasting blood sugar" or "body weight" or "weigh gain" or "hypoglycemia." Also, gray literature sources such as meeting abstracts, ClinicalTrials.gov, the American diabetes association, and the international diabetes federation websites were searched. The time and language of publications were not restricted. In addition, we contacted experts and other researchers in the field for ongoing studies and additional data using Email and by reviewing the reference lists of retrieved publications for additional pertinent studies. Duplicate publications were removed. Our complete search strategy is available in Data S2. Two authors (MD and MS) independently screened the studies based on titles and abstracts and finally, the full texts were reviewed in case the studies met the inclusion criteria based on the title and abstract.

Selection criteria

In the current systematic review and meta-analysis, based on our PICO, we included RCTs conducted on patients with uncontrolled type 2 diabetes (HbA1c $\geq$ 7%), regardless of their baseline T2D treatment (oral antidiabetics with or without insulin therapy). RCTs were included if they compared basal-bolus insulin regimens with premixed insulin regimens with a treat-to-target approach (i.e., appropriate dose intensification to reach glycemic targets; HbA1c < 7% or FPG < 126 mg/dL) for the following four outcomes: differences in HbA1c, fasting plasma glucose (FPG), weight gain, and odds of hypoglycemia (including both overall hypoglycemia and nocturnal hypoglycemia). An adequate and standard randomization process was a key inclusion criterion. Studies were included if the treatment arms had comparable baseline variables, including the duration of diabetes, mean age, HbA1c level, and body mass index. Studies in which the treatment arms differed in terms of concomitant interventions were excluded. Only studies that assessed people with T2DM were included, and studies related to type 1 diabetes, gestational diabetes, and diabetes caused by other factors were excluded. RCTs were included only if they had a minimal follow-up duration of 12 weeks.

Additionally, RCTs were excluded if they included patients with advanced cardiovascular or renal diseases (e.g., recent myocardial infarction, stroke, severe heart failure, end-stage renal disease) or recent severe cardiovascular events to avoid confounding effects. While diabetes itself is a risk factor for cardiovascular and renal diseases, the focus was on excluding those with very high-risk profiles or unstable conditions.

When multiple studies were published from the same trial with the same population, only the latest study (provided it had the largest sample size, comprehensive patient data, and complete and accurate outcome reporting) was included. The process of identifying, screening, and selecting phase three randomized clinical trials for the systematic review and meta-analysis is schematically shown in Figure 1. A list of excluded articles after full-text review is also available in Table S1.

Data extraction and risk of bias assessment

The main characteristics that were extracted from eligible randomized clinical trial studies included the following: author name, publication year, name of the country, gender, mean, standard deviation or age range of the patients, study setting and population, duration of follow-up of patients (weeks), type of diabetes, diabetes duration (year), number of patients in each treatment group, prescribed treatment (in both groups) and dose, study outcomes (HbA1c, FPG, body weight, and

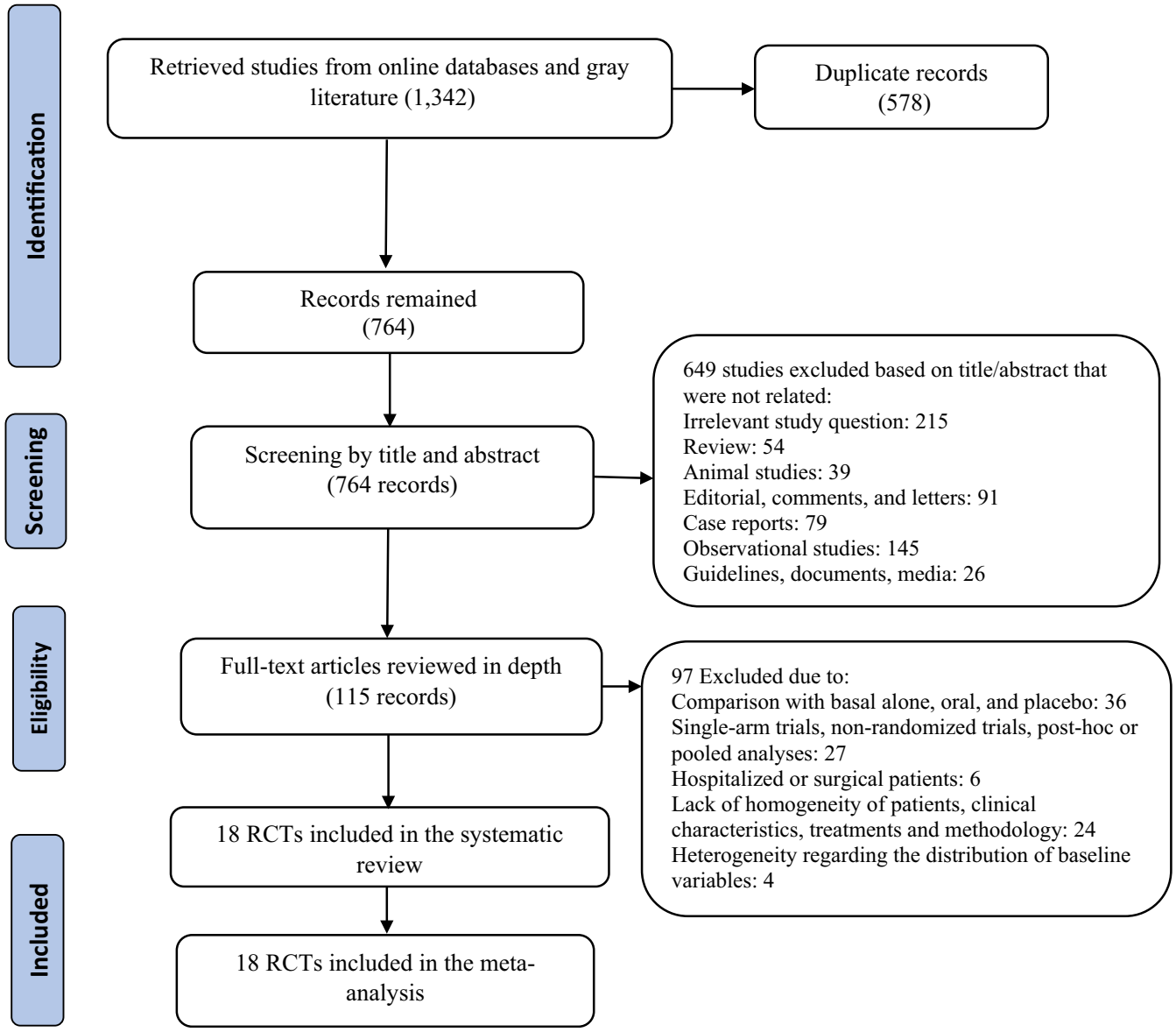

Figure 1 | Flowchart for selection of studies.

hypoglycemia), effect size estimates (odds ratio or mean difference) and their 95% confidence intervals, baseline values of age, body weight, body mass index, fasting blood sugar, and HbA1c in both groups. The data were extracted independently by two researchers (MD and MS) and the observed differences were resolved by consensus with the supervisor.

To assess the risk of bias or methodological quality of included RCTs, the new and revised Cochrane risk of bias tool (ROB-2) was used[20]. The tool includes five domains; each domain contains several questions, and the answer to each question has five options (yes, probably yes, probably no, no, no information). At the end of each domain, a risk of bias judgment is made for the domain as either low risk of bias, some concerns, or high risk of bias. Finally, an overall judgment of the risk of bias is made for each study which is the final summary of all five domains[20]. Two reviewers (MD and MS) assessed the risk of bias in studies and two reviewers (HRB and FB) verified it.

Statistical analysis

The premixed regimen versus basal-bolus regimen was compared in all studies. The null hypothesis (H_0) posits that there is no significant difference in efficacy and safety between premixed and basal-bolus regimens. The alternative hypothesis (H_1) posits that one regimen provides superior outcomes compared with the other. Statistical equivalence was assessed using random-effects

Table 1 | Main characteristics of 18 randomized controlled trials comparing premixed with basal-bolus insulin regimens in T2DM patients

Study, year	Country	Background therapy	Duration of DM (year)	Follow-up (week)	Baseline BMI	Baseline HbA1c (%)	Mean age (year)	ROB	Treatment (1)	Sample size	Treatment (2)	Sample size
Philis-Tsimikas, 2019	Seven countries	Basal insulin ± OADs	12.9	38	31.7	8.15	58.69	Low risk	IDegAsp	267	IGlar+IAsp	265
Rodbard, 2016	USA	Basal insulin ± OADs	12.5	26	32.1	8.3	59.6	Low risk	IDegAsp	138	IDeg+IAsp	136
Jin, 2016	South Korea	Basal insulin ± OADs	15.68	24	24.53	8.39	59.5	High risk	Novolog Mix	82	IGlar+IGlu	78
Vora, 2015	Australia and UK	Basal insulin ± OADs	12.95	24	31.1	8.61	61.6	Low risk	BIAsp	165	IGlar+IGlu	170
Malek, 2015	Four African countries	Basal insulin ± OADs	7.5	50	29.75	8.65	52.8	Low risk	BIAsp	192	IDet+IAsp	185
Jia, 2015	China, Taiwan, and Korea	Insulin naïve patients	15.2	24	26.5	8.65	58.6	Low risk	Humalog Mix	197	IGlar+ILisp	202
Tinahones, 2014	Multinational	Premixed insulin ± OADs	11.75	24	29.6	8.65	57.5	Low risk	Humalog Mix	236	IGlar+ILisp	240
Riddle, 2014	USA	Basal insulin ± OADs	9.3	60	33.2	9.4	53.7	Some concerns	Novolog Mix	194	IGlar+IGlu	194
Shanmugasunda, 2012	India	Insulin naïve patients	13.65	12	30.22	9.2	53.9	High risk	BHI	25	IDet+IAsp	25
Bowering, 2012	Seven countries	Premixed insulin + OADs	10.29	48	27.69	9	56.48	Some concerns	Humalog Mix	211	IGlar+ILisp	212
Liebl, 2009	Austria, Germany and Switzerland	OADs without insulin in past 90 days	9.15	26	30.8	8.45	61	Some concerns	BIAsp	178	IDet+IAsp	537
Ligthelm, 2006	13 Countries (10 Europe and three Asian)	OADs ± basal insulin	13.5	16	29.35	9.1	59.65	Low risk	BIAsp	196	NPH + IAsp	198
Rosenstock, 2008	USA and Puerto Rico	Insulin[†]± OADs	11	24	34.5	8.8	55	Low risk	Humalog Mix	187	IGlar+ILisp	187
Miser, 2010	Five countries	Basal insulin + OADs	9.8	26	33.2	8	55	Low risk	Humalog Mix	174	IGlar+ILisp	171
Fritsche, 2010	Europe and Australia	Insulin[†]± OADs	12.6	52	30	8.5	60.5	Low risk	BHI	157	IGlar+IGlu	153
Jain, 2010	Nine countries	Premixed insulin ± OADs	11.7	36	29	9.4	59.4	Low risk	Humalog Mix	188	IGlar+ILisp	195
Levin, 2011	USA	Insulin naïve patients	13	38	35.8	9.3	56.2	Some concerns	BIAsp	91	IGlar+IGlu	106
Giugliano, 2014	Nine countries	Insulin[†] or OADs	12.2	48	29.4	9.1	54.3	Low risk	Humalog Mix	171	IGlar+ILisp	173

OAD, Oral antidiabetic drug. [†]Regardless of type.

models, and clinical significance was interpreted based on effect sizes and confidence intervals. The main outcomes were HbA1c (decrease from baseline at the end of treatment), FPG, weight change, and hypoglycemic events. All included studies reported HbA1c, FPG, and body weight as continuous variables and reported mean, standard deviation, and sample size in each group. For continuous outcomes (HbA1c, FPG, and body weight), the weighted mean differences (WMD) were calculated based on the raw data from individual studies, which included sample size, mean, and standard deviation. For dichotomous outcomes (hypoglycemic events), pooled odds ratios (OR) were calculated from the raw data, including sample size and number of events in each group (number of patients experiencing hypoglycemia). Pooled estimates with their corresponding 95% CIs were calculated using Der-Simonian and Laird and inverse-variance weights methods[21]. Forest plots were used to visually assess the heterogeneity of the pooled WMDs for continuous variables and pooled ORs for dichotomous outcomes.

I^2 statistics was used to assess the heterogeneity across studies[22] ($I^2 = 0\%$ indicates no observed heterogeneity and $I^2 \geq 50\%$ indicates substantial heterogeneity). Cochran's Q statistic was also used to analyze the statistical significance of heterogeneity[23]. Sensitivity analysis was performed to determine which study (if any) had the largest impact on the heterogeneity and to assess the robustness of pooled estimates. Subgroup analyses (based on ROB and BMI category) were conducted only for HbA1c and FPG (and not for other outcomes) due to the considerable heterogeneity that was observed. Moreover, subgroup analyses were conducted to evaluate the effects of the interventions in insulin-naïve patients and those already receiving insulin separately. Visual inspection of funnel plots was done to assess publication bias[24]; MD or OR was plotted against the inverse of the square of the standard error. All statistical tests were two-tailed, and the significance level was set at <0.05 for all, except for the heterogeneity test. Statistical analyses were performed using Stata version 17.0 (Stata Corp., College Station, TX, USA).

Rating the quality and strength of the evidence

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the overall quality of the evidence for each outcome[25]. The evidence-quality ratings range from high to very low. Evidence from RCTs starts as high-quality evidence; It is then either rated down for features including the risk of bias, imprecision, indirectness, inconsistency, and publication bias or rated up based on plausible confounding or the presence of dose–response relationships[25].

Table 2 | Revised Cochrane risk of bias assessment tool (ROB-2) for included RCTs

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall Bias
Philis-Tsimikas A, 2019	+	+	?	?	+	+
Rodbard HW, 2016	+	?	+	+	+	+
Vora J, 2015	+	+	?	+	+	+
Malek R, 2015	+	+	?	+	+	+
Jia W, 2015	+	+	?	+	+	+
Riddle MC, 2014	+	?	?	?	+	?
Rosenstock, 2008	+	+	+	+	+	+
Giugliano, 2014	+	+	+	+	+	+
Shanmugasundar G, 2012	−	−	?	?	+	−
Bowering K, 2012	?	?	?	?	+	?
Levin, 2011	+	?	+	?	?	?
Ligthelm RJ, 2006	+	?	?	+	+	+
Miser WF, 2010	+	?	?	+	+	+
Jain, 2010	+	?	?	+	+	+
Fritsche A, 2010	+	?	?	+	+	+
Liebl A, 2009	?	?	+	+	?	?
Tinahones FJ, 2014	+	+	+	+	+	+
Jin SM, 2016	+	?	−	?	−	−

+ Low Risk ? Some Concerns − High Risk

RESULTS

Descriptive results

We identified 1,342 records through comprehensive and systematic database searching. Five hundred- and-forty-nine (549) records remained after removing duplicates and studies that were unrelated to the research question according to title. After removing the studies not meeting the eligibility criteria, 115 full texts were assessed. We then selected 18 studies for the systematic review based on the defined criteria including the study intervention, outcomes, methodological characteristics, and the clinical and baseline characteristics of the patients. All 18 RCTs were included in the meta-analysis. Notably, several studies directly compared basal insulin alone (without bolus) with premixed insulin and were not included in the present systematic review.

Table 1 demonstrates the main characteristics of the 18 RCT that were included in the systematic review[13–18,26–37]. The included trials were published between 2006 and 2019. Most of the trials were multicenter and multinational from all continents and with relatively large sample sizes. Only one study had a total sample size of smaller than 100 subjects, that is, <50 patients in each group. No study was conducted as a crossover clinical trial design, and all of them were parallel clinical trials.

Both men and women were included in all studies. The mean age of patients in studies related to T2DM was 57.7 years (range 61.6– 52.8 years). The mean treatment period (follow-up period) was 31 weeks and the mean duration of T2DM was 12.1 (range 15.7–7.5) years. The mean HbA1c level and body mass index (BMI) at baseline were 8.7% (range 9.4–8.1%) and 29.7 (range 24.5–35.8), respectively.

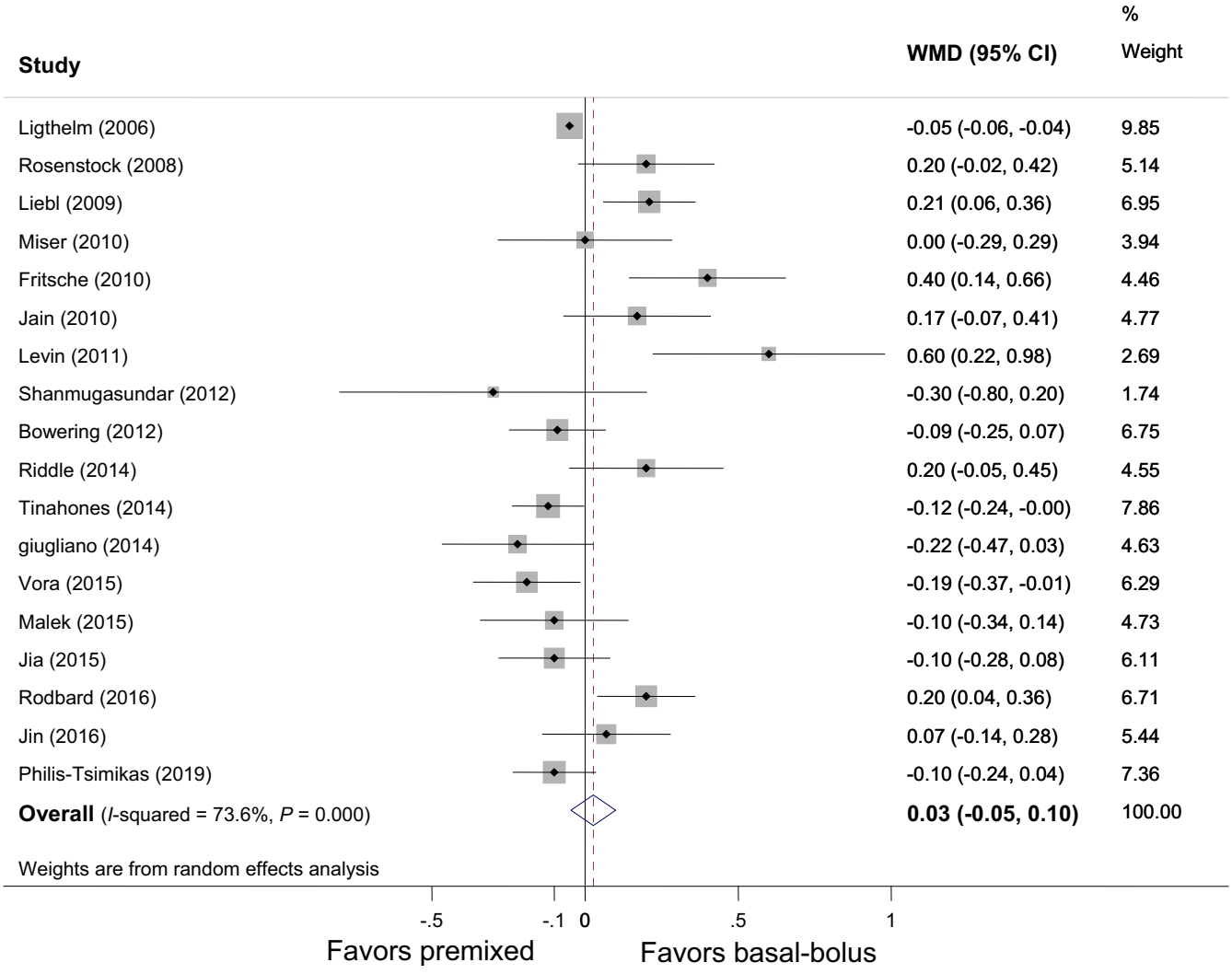

Figure 2 | Forest plot of the mean difference in HbA1c (HbA1c decrease from baseline, %) in all 18 randomized controlled trials comparing premixed insulin versus basal-bolus regimen for type 2 diabetes.

Risk of bias assessment

All 18 clinical trials were assessed for methodological quality, the results of which are presented in full detail in Table 2. Based on the assessment, two RCTs (11% of studies) were at high risk of bias, four RCTs (23% of studies) posed some concerns at risk of bias, and 12 RCTs (66% of the studies) were placed in the low risk of bias category. More than half of the studies had low risk of bias because of their standard design, conduct, analysis, and reporting. Less than half of the studies had insufficient explanations regarding the three items that raised concerns regarding the risk of bias: deviations from the intended interventions, missing outcome data, and the measurement of the outcome data. Although the proportion of missing outcome data and the reasons for missingness were similar in the comparison groups, it was possible that the findings were biased by the missing data.

Main findings of the outcomes

Figure 2 displays the WMD in HbA1c (HbA1c decrease from baseline, %) in all 18 RCTs comparing premixed insulin versus basal-bolus regimen for T2DM. Three of the 18 studies reported a superior effect for premixed insulin, whereas four studies reported the basal-bolus regimen was superior in terms of reducing HbA1c. The random-effects meta-analysis showed that there is no significant clinical difference in the efficacy of basal-bolus insulin regimen compared with premixed insulin regimen regarding the reduction of HbA1c levels in people with T2DM in the intensification therapy. Therefore, both regimens have the same efficacy (pooled mean difference, WMD: 0.03%; 95% CI: −0.05%, 0.10%; Moderate Certainty Evidence). Heterogeneity was significant across studies ($P < 0.001$ (Q statistics), $I^2 = 73.6\%$) but this was unlikely to affect the pooled estimate. In a sensitivity analysis by successively removing a particular study at a time to assess the influence of every single study on the pooled estimate, a nonsignificant difference was observed consistently (range of summary WMDs: 0.01–0.04), which did not alter the pooled results, indicating the robustness of our meta-analysis model (Figure S1). Due to observed heterogeneity across the studies, the meta-analysis was repeated to only include the studies at low risk of bias. The results were not

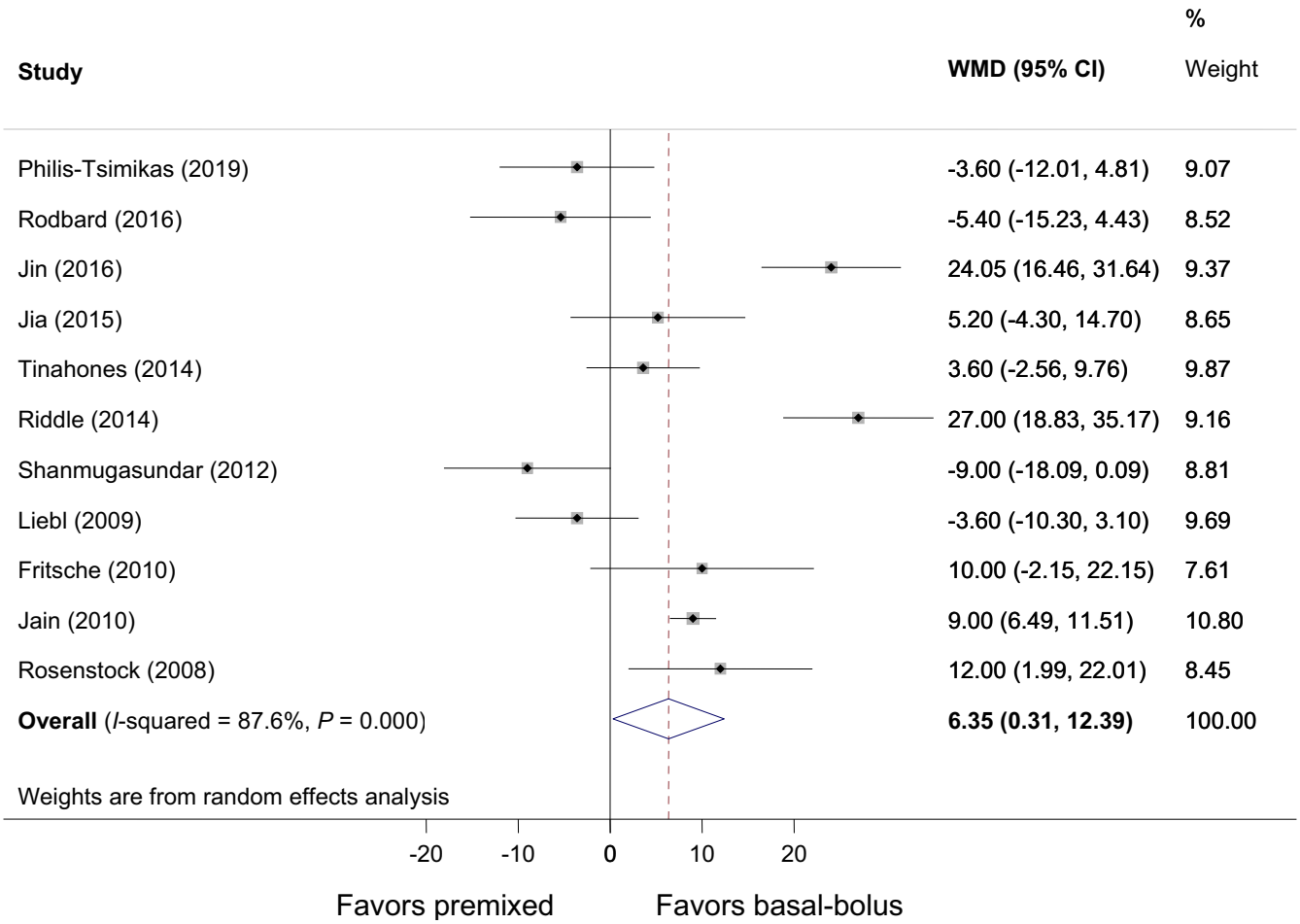

Figure 3 | Forest plot of the mean difference in fasting plasma glucose (premixed insulin vs. basal-bolus regimen) for type 2 diabetes.

significant in favor of either of the two insulin regimens regarding the decrease in the mean HbA1c (WMD: 0.03; 95% CI: −0.09, 0.07). In a subgroup meta-analysis based on baseline BMI, findings showed no significant clinical difference in the efficacy of premixed insulin compared with the basal-bolus regimen (WMD for baseline BMI ≤ 30: −0.03; 95% CI: −0.11, 0.05 and WMD for baseline BMI > 30: 0.09; 95% CI: −0.05, 0.23). Begg's adjusted rank correlation test ($P = 0.12$) and Egger's regression asymmetry test ($P = 0.10$) indicated that publication bias is unlikely (Figure S2).

Regarding the FPG, meta-analysis findings indicated that treatment with a basal-bolus regimen provided greater improvement in FPG than premixed regimens for people with T2DM (WMD: 6.35 mg/dL; 95% CI: 0.31, 12.39 mg/dL; Figure 3). However, our confidence in this finding was low due to the possible effects of inconsistency and imprecision on the calculated effect estimate (Table 3). Significant heterogeneity was observed across studies ($P < 0.001$ (Q statistics), $I^2 = 87.6\%$). Sensitivity analysis showed consistency of the significant difference which indicated the robustness of meta-analysis findings. Figure 4 shows the meta-analysis results for comparing the premixed insulin with the basal-bolus regimen for their effect on body weight. Findings showed that the regimens have similar effects on weight gain (WMD: 0.12 kg; 95% CI: −0.99, 1.23 kg; High certainty evidence).

The meta-analysis showed that the basal-bolus regimen and premixed insulins are similar regarding the odds of developing overall, nocturnal, and severe hypoglycemia (Pooled OR: 0.9; 95% CI: 0.94, 1.04, High certainty evidence; Pooled OR: 1.02; 95% CI: 0.93, 1.11, High certainty evidence; Pooled OR: 1.00;

Table 3 | Summary of findings; Premixed insulin compared with basal-bolus insulin for intensification of insulin therapy in people with T2DM

Patient or population: intensification of insulin therapy in people with type 2 diabetes

Intervention: Premixed insulin

Comparison: Basal-bolus insulin

Outcomes	■ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with Basal-bolus insulin	Risk difference with Premixed insulin
Hemoglobin A1C decrease from baseline (Hb A1c) follow-up: range 12–60 weeks	6,476 (18 RCTs)	⊕⊕⊕◯ Moderate[†]	–	The mean hemoglobin A1C decrease from baseline was 0	MD 0.03 higher (0.05 lower to 0.1 higher)
Mean difference in fasting plasma glucose (FPG) follow-up: range 12–60 weeks	3,902 (11 RCTs)	⊕⊕◯◯ Low[‡,§]	–	The mean Difference in Fasting Plasma Glucose was 0 mg/dL	MD 6.35 mg/dL more (0.31 more to 12.39 more)
Mean difference in body weight follow-up: range 12–60 weeks	5,699 (16 RCTs)	⊕⊕⊕⊕ High	–	The mean Difference in Body Weight was 0 kg	MD 0.12 kg higher (0.99 lower to 1.23 higher)
Overall hypoglycemia follow-up: range 12–52 weeks	5,247 (14 RCTs)	⊕⊕⊕⊕ High	OR 0.99 (0.94–1.04)	608 per 1,000	2 fewer per 1,000 (15 fewer to 9 more)
Nocturnal hypoglycemia follow-up: range 12–52 weeks	4,689 (13 RCTs)	⊕⊕⊕⊕ High	OR 1.02 (0.93–1.11)	267 per 1,000	4 more per 1,000 (14 fewer to 21 more)
Severe hypoglycemia follow-up: range 12–52 weeks	4,731 (10 RCTs)	⊕⊕⊕◯ Moderate[¶]	OR 1.00 (0.74–1.35)	36 per 1,000	0 fewer per 1,000 (9 fewer to 12 more)

GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [†]Significant heterogeneity among the studies. [‡]The results of the studies are heterogeneous and this issue has likely impacted the pooled effect estimate for this outcome. [§]The pooled effect estimate covers a range from not clinically significant to considerable clinical significance. [¶]Downrated for precision due to the small number of total event rates, and the confidence interval of the pooled estimate that covers an odds ratio range from 0.75 to 1.35. CI, confidence interval; MD, mean difference; OR, odds ratio.

95% CI: 0.74, 1.35 respectively, Moderate certainty evidence; Figures 5–7). Heterogeneity was not observed across the studies for the hypoglycemia-related outcomes (P = 0.61–0.98 (Q statistics), I^2 = 0.0% for all three analyses). Consistently nonsignificant differences were observed using sensitivity analysis. Subgroup meta-analysis by baseline BMI and restricting the analyses to low risk of bias studies did not alter the pooled results.

Subgroup analyses were conducted for all study outcomes to evaluate the effects of the interventions in insulin-naïve patients and those already receiving insulin in the included studies separately. All findings were consistent with our main results regardless of background antidiabetic therapy in patients for all outcomes except FPG, where greater improvement in FPG was observed only in patients already receiving insulin (WMD: 9.67 mg/dL; 95% CI: 2.86, 16.49 mg/dL) and not insulin naïve patients in basal-bolus group versus premixed (Figures S3–S7). The overall effect estimates and the certainty of the evidence for each outcome are presented in Table 3.

DISCUSSION

Findings from the present systematic review and meta-analysis showed that there is no statistically and clinically relevant difference in the efficacy of premixed insulin versus basal-bolus regimens for HbA1c decrease in people with T2DM in the intensification stage of insulin therapy. Our findings showed that treatment with a basal-bolus regimen provided a slightly greater improvement in FPG than premixed regimens; Although this reduction in fasting does not seem to be clinically important and the overall confidence in this finding was low. Importantly, the treatment regimens did not show different rates of adverse events including weight gain and hypoglycemia. The equivalence observed in our study can be attributed to the treat-to-target design of the included trials, which optimized glycemic control in both treatment arms through dose adjustments. This underscores the importance of patient preference and individualized care when choosing between the two regimens.

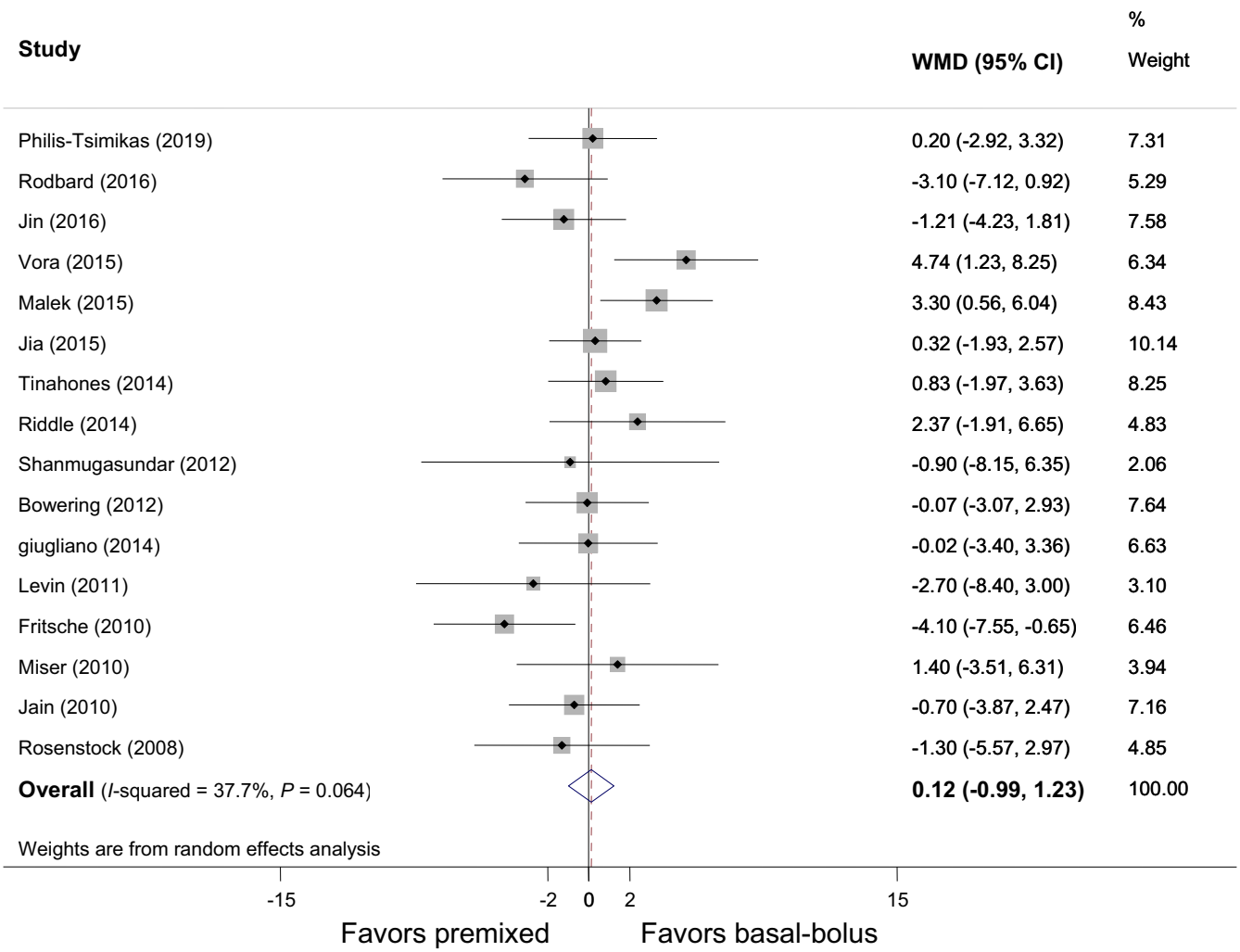

Figure 4 | Forest plot for the mean difference in body weight (premixed insulin vs. basal-bolus regimen) for type 2 diabetes.

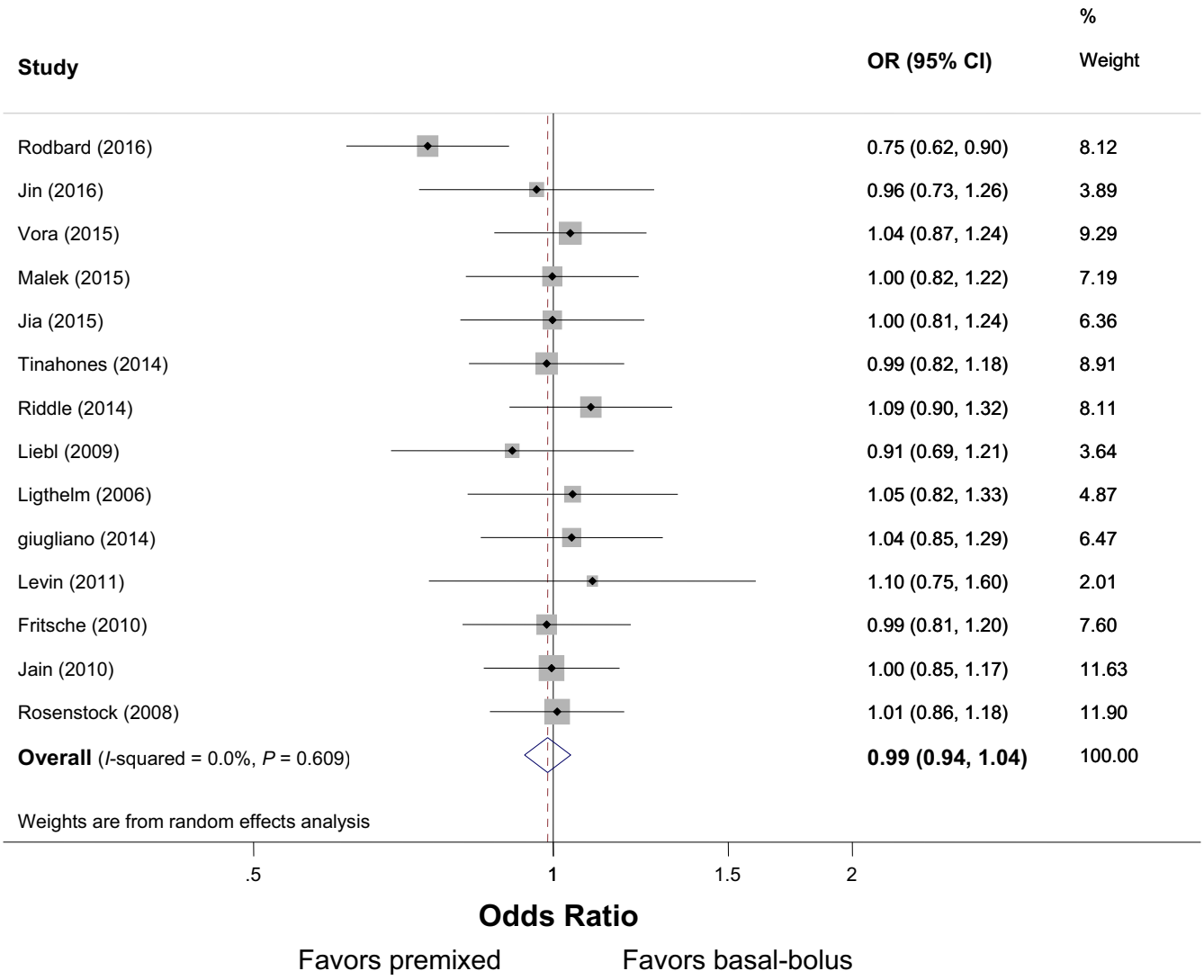

Figure 5 | Forest plot of the odds ratio of any/overall hypoglycemia (premixed insulin vs. basal-bolus regimen) for type 2 diabetes.

There was significant heterogeneity across studies regarding the efficacy but not safety outcomes. Sensitivity and subgroup analyses based on pre-specified study-level characteristics did not reveal any source of heterogeneity[38]. It remained unexplained and therefore is assumed to be related to the conceptual and also the clinical characteristics of the patients, therefore, a random-effects model was used to generate pooled estimates[38,39]. This can better guide clinical and policy decisions[8,40].

Our findings offer the best available evidence to support similar glycemic control and safety with premixed insulin and basal-bolus regimens for intensification of insulin therapy in people with T2DM. In a meta-analysis of 13 RCTs in 2016, a change in HbA1c level between basal-bolus and premixed insulin regimens resulted in a small and nonsignificant difference of 0.09%. There was no significant difference in the event rate for overall hypoglycemia, weight change, and daily insulin dose. The likelihood for reaching the HbA1c target was 8% higher with the basal-bolus as compared with the premixed regimen[41]. The findings of the present updated meta-analysis, which was conducted on 18 RCTs with considerable sample sizes, were consistent with those of the previous meta-analysis regarding most of the investigated outcomes, although, the reduction in fasting blood sugar was in favor of basal-bolus. Additionally, our study utilized the updated Cochrane ROB-2 tool for rigorous quality assessment, which was not employed in earlier analyses, and the GRADE approach to evaluate the certainty of evidence, further enhancing the reliability of our findings. Moreover, our subgroup analyses focusing on insulin-naïve patients and those already using insulin provided new insights into these distinct populations. A meta-analysis with few studies in 2011 concluded that treatment with a premixed insulin regimen resulted in a lower chance of reaching the HbA1c target

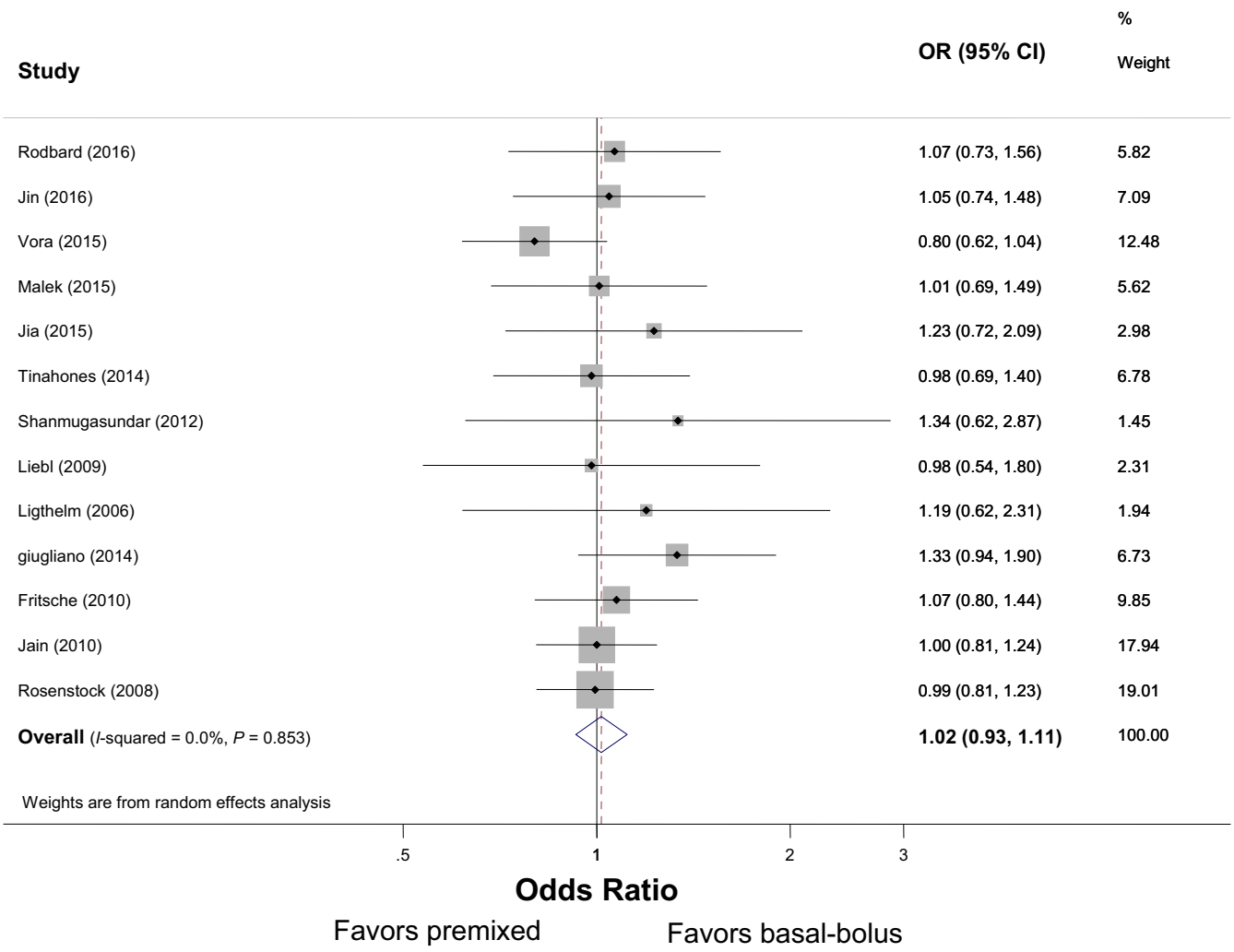

Figure 6 | Forest plot of the odds ratio of nocturnal hypoglycemia (premixed insulin vs. basal-bolus regimen) for type 2 diabetes.

compared with a basal-bolus regimen[42]. However, their approach differed in that they assessed the rate of achieving an HbA1C goal in contrast to the mean difference from baseline in our study. Their comparisons were also more heterogeneous compared with the current systematic review. Their findings were consistent with our findings regarding the lack of difference in the incidence of hypoglycemia or weight gain between the two regimens.

Our systematic review was limited to RCTs, the results of which may not be applicable in a real-world setting. However, in a retrospective cohort study that compared real-world outcomes, there was no significant difference in clinical HbA1c reduction from baseline and the incidence of hypoglycemia in people with T2DM treated with insulin glargine and bolus insulin (basal-bolus regimen) compared with those who switched to a premixed insulin regimen[43]. Switching from one insulin intensification regimen to another is a strategy to increase the number of patients reaching the desired target. The findings of the A1chieve trial[44] seem to support this strategy. Glycemic control significantly improved in patients who switched from basal-bolus insulin regimens to biphasic insulin aspart (BIAsp); hypoglycemia significantly decreased after 24 weeks. Conversely, in another study, when people with T2DM switched from premixed insulin to basal insulin glargine plus rapid-acting insulin experienced significant improvements in HbA1c, without an increase in hypoglycemia or body weight[45].

The heterogeneity in the observed differences between the two regimens points to a possible role of the patient's individual characteristics. Personalized treatment is further supported by the beneficial effect of switching between basal-bolus insulin regimens and premixed insulin regimens or vice versa in patients who do not meet treatment goals[46].

Premixed insulin regimens are among the insulin treatment plans that are prescribed both in patients without a history of receiving insulin and in patients already receiving insulin who need more intensive treatment[46]. In the present systematic

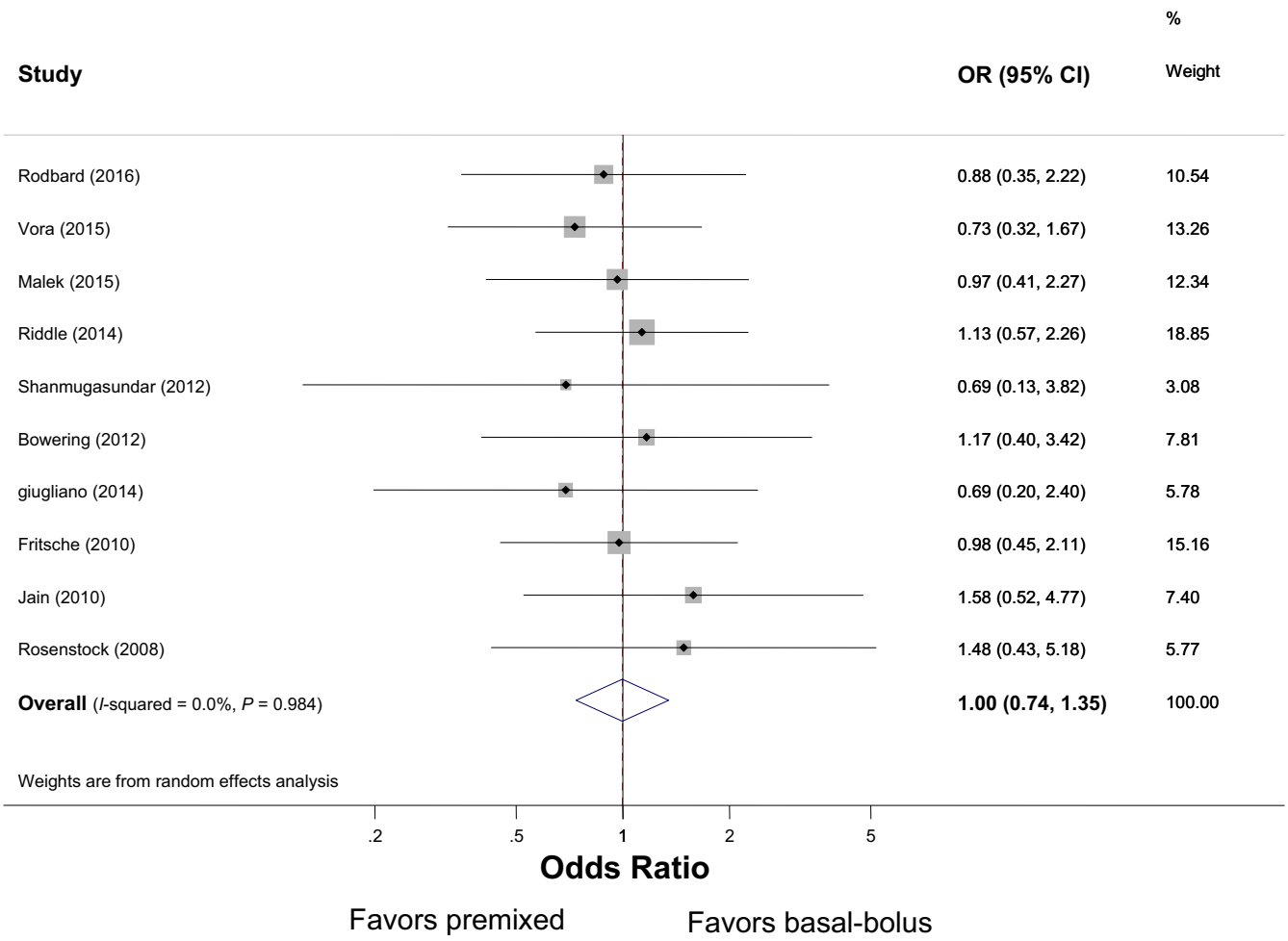

Figure 7 | Forest plot for the odds ratio of severe hypoglycemia (premixed insulin vs. basal-bolus regimen) for type 2 diabetes.

review, we included patients with a history of insulin therapy with basal who needed to intensify the treatment with basal-bolus or premixed insulin in order. Therefore, studies comparing the premixed with basal insulin alone were outside the scope of this review.

It should be noted that the definition of any/overall hypoglycemia was not uniform among the eligible studies (ranging from incidence of symptoms typically associated with hypoglycemia with or without plasma glucose level of 3.9 mmol/L or less to confirmed blood glucose level of 3.9 mmol/L or less), which somewhat reduces the applicability of the findings of the present study to clinical practice. The daily insulin dosing regimens also differed among the included studies, so the results should be interpreted with caution.

This systematic review had many advantages. The measurement of study outcomes (HbA1c, FPG, weight gain, and hypoglycemia including overall and nocturnal hypoglycemia) was standardized among all included studies, and studies that used a non-standardized measurement were excluded from the analysis. The multinational nature of the study population and the broad age range of participants make the results highly relevant to the global population with T2DM. Also, sensitivity analyses were performed by considering and limiting the analyses to studies with good quality (low risk of bias) and studies with adequate sample size. These analyses led to the robustness and consistency of the meta-analysis model. The low probability of publication bias indicated a relatively comprehensive search for randomized clinical trials.

Regarding the quality of the included studies, deviations from the intended interventions, missing outcome data, and problems with measurement of the outcome data were three main concerns. We recommend that researcher consider these issues to minimize biases in the design and conduct of future clinical trials. There were no considerable problems related to randomization process among the studies.

The findings of this meta-analysis support the notion that there is no clinically significant difference in the efficacy of premixed insulins compared with basal-bolus regimens in achieving

adequate glycemic control specifically in the context of treatment intensification for people with T2DM. The same is true for safety outcomes, including body weight and hypoglycemia. Neither premixed insulins nor basal-bolus regimens showed a consistent advantage in terms of both efficacy and safety. Clinicians should adopt an individualized approach to insulin intensification, taking into account patient preferences and the benefits and risks of the regimens in individual patients. Our findings provide a framework to guide decision-making in real-world settings, emphasizing the importance of personalized treatment plans.

FUNDING

Vice-Chancellor for Research of Iran University of Medical Sciences provided financial support for the conduct of the present research (Grant number: 111937). The funder had no role in conducting the systematic review and funding has not been received from manufacturers of treatments in the research.

ACKNOWLEDGMENTS

Authors would like to thank Ms. Roya Vesal Azad as an information specialist for her assistance in the systematic searching of the databases.

DISCLOSURE

The authors declare no conflict of interest.
Approval of research protocol: N/A.
Informed consent: N/A.
Approval of the research protocol: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

REFERENCES

1. Saeedi P, Petersohn I, Salpea P, *et al*. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas. *Diabetes Res Clin Pract* 2019; 157: 107843.
2. American Diabetes Association 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44(Suppl 1): S15–S33.
3. Burrows NR, Li Y, Gregg EW, *et al*. Declining rates of hospitalization for selected cardiovascular disease conditions among adults aged ≥35 years with diagnosed diabetes, U.S., 1998–2014. *Diabetes Care* 2018; 41: 293–302.
4. American Diabetes Association Professional Practice Committee: 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2022. *Diabetes Care* 2022; 45: S125–S143.
5. Baena-Díez JM, Penafiel J, Subirana I, *et al*. Risk of cause-specific death in individuals with diabetes: A competing risks analysis. *Diabetes Care* 2016; 39: 1987–1995.
6. Morello CM. Pharmacokinetics and pharmacodynamics of insulin analogs in special populations with type 2 diabetes mellitus. *Int J Gen Med* 2011; 4: 827–835.
7. Meneghini LF. Intensifying insulin therapy: What options are available to patients with type 2 diabetes? *Am J Med* 2013; 126: S28–S37.
8. Garber AJ, Abrahamson MJ, Barzilay JI, *et al*. Consensus statement by the American Association of Clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. *Endocr Pract* 2016; 22: 84–113.
9. Ampudia-Blasco FJ, Rossetti P, Ascaso JF. Basal plus basal-bolus approach in type 2 diabetes. *Diabetes Technol Ther* 2011; 13(Suppl 1): S75–S83.
10. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. *Diabetes Care* 2017; 40 (Suppl 1): S64–S74.
11. Pettus J, Santos Cavaiola T, Tamborlane WV, *et al*. The past, present, and future of basal insulins. *Diabetes Metab Res Rev* 2016; 32: 478–496.
12. Porcellati F, Lucidi P, Bolli GB, *et al*. GlP-1 RAs as compared to prandial insulin after failure of basal insulin in type 2 diabetes: Lessons from the 4B and get-goal DUO 2 trials. *Diabetes Metab* 2015; 41: 6s16–6s20.
13. 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.
14. Philis-Tsimikas A, Astamirova K, Gupta Y, *et al*. Similar glycaemic control with less nocturnal hypoglycaemia in a 38-week trial comparing the IDegAsp co-formulation with insulin glargine U100 and insulin aspart in basal insulin-treated subjects with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2019; 147: 157–165.
15. Giugliano D, Tracz M, Shah S, *et al*. Initiation and gradual intensification of premixed insulin lispro therapy versus basal ± mealtime insulin in patients with type 2 diabetes eating light breakfasts. *Diabetes Care* 2014; 37: 372–380.
16. Rosenstock J, Ahmann AJ, Colon G, *et al*. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: Prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care* 2008; 31: 20–25.
17. Ligthelm RJ, Mouritzen U, Lynggaard H, *et al*. Biphasic insulin aspart given thrice daily is as efficacious as a basal-bolus insulin regimen with four daily injections. *Exp Clin Endocrinol Diabetes* 2006; 114: 511–519.
18. Rodbard HW, Cariou B, Pieber TR, *et al*. Treatment intensification with an insulin degludec (IDeg)/insulin aspart (IAsp) co-formulation twice daily compared with basal IDeg and prandial IAsp in type 2 diabetes: A randomized, controlled phase III trial. *Diabetes Obes Metab* 2016; 18: 274–280.

19. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *Ann Intern Med* 2009; 151: 264–269.
20. Sterne JA, Savović J, Page MJ, *et al*. Rob 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 28: 366.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
22. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Chichester: The Cochran Collaboration, 2011.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
24. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
25. Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–992.
26. Malek R, Ajili F, Assaad-Khalil SH, *et al*. Similar glucose control with basal–bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification. *Diabetes Metab* 2015; 41: 223–230.
27. Tinahones FJ, Gross JL, Onaca A, *et al*. Insulin lispro low mixture twice daily versus basal insulin glargine once daily and prandial insulin lispro once daily in patients with type 2 diabetes requiring insulin intensification: A randomized phase IV trial. *Diabetes Obes Metab* 2014; 16: 963–970.
28. Riddle MC, Rosenstock J, Vlajnic A, *et al*. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: Twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes Obes Metab* 2014; 16: 396–402.
29. Bowering K, Reed VA, Felicio J, *et al*. A study comparing insulin lispro mix 25 with glargine plus lispro therapy in patients with type 2 diabetes who have inadequate glycemic control on oral anti-hyperglycemic medication: Results of the PARADIGM study. *Diabet Med* 2012; 29: e263–e272.
30. Levin PA, Zhang Q, Mersey JH, *et al*. Glycemic control with insulin glargine plus insulin glulisine versus premixed insulin analogues in real-world practices: A cost-effectiveness study with a randomized pragmatic trial design. *Clin Ther* 2011; 33: 841–850.
31. Fritsche A, Larbig M, Owens D, *et al*. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes—Results of the GINGER study. *Diabetes Obes Metab* 2010; 12: 115–123.
32. Miser WF, Arakaki R, Jiang H, *et al*. Randomized, open-label, parallel-group evaluations of basal-bolus therapy versus insulin lispro premixed therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral antihyperglycemic drugs: A noninferiority intensification substudy of the DURABLE trial. *Clin Ther* 2010; 32: 896–908.
33. Jain SM, Mao X, Escalante-Pulido M, *et al*. Prandial–basal insulin regimens plus oral antihyperglycaemic agents to improve mealtime glycaemia: Initiate and progressively advance insulin therapy in type 2 diabetes. *Diabetes Obes Metab* 2010; 12: 967–975.
34. Liebl A, Prager R, Binz K, *et al*. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER study: A randomized controlled trial. *Diabetes Obes Metab* 2009; 11: 45–52.
35. 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.
36. Vora J, Cohen N, Evans M, *et al*. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: A 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). *Diabetes Obes Metab* 2015; 17: 1133–1141.
37. Shanmugasundar G, Bhansali A, Walia R, *et al*. Comparison of thrice daily biphasic human insulin (30/70) versus basal detemir & bolus aspart in patients with poorly controlled type 2 diabetes mellitus–a pilot study. *Indian J Med Res* 2012; 135: 78–83.
38. Cordero CP, Dans AL. Key concepts in clinical epidemiology: Detecting and dealing with heterogeneity in meta-analyses. *J Clin Epidemiol* 2021; 130: 149–151.
39. Deeks JJ, Higgins JPT, Altman DG, *et al*. (eds). Analyzing data and undertaking meta-analyses: heterogeneity. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Chichester, West Sussex; Hoboken NJ: John Wiley & Sons, 2008.
40. Borenstein M, Higgins JPT, Hedges LV, *et al*. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017; 8: 5–18.
41. Giugliano D, Chiodini P, Maiorino MI, *et al*. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Endocrine* 2016; 51: 417–428.
42. Giugliano D, Maiorino MI, Bellastella G, *et al*. Efficacy of insulin analogs in achieving the hemoglobin A1c target of <7% in type 2 diabetes: Meta-analysis of randomized controlled trials. *Diabetes Care* 2011; 34: 510–517.
43. Miao R, Wei W, Baser O, *et al*. Real world outcomes of adding rapid-acting insulin versus switching to analog premix insulin among US patients with type 2 diabetes treated with insulin glargine. *Patient Prefer Adherence* 2013; 7: 951.
44. Dieuzeide G, Chuang LM, Almaghamsi A, *et al*. Safety and effectiveness of biphasic insulin aspart 30 in people with

type 2 diabetes switching from basal-bolus insulin regimens in the A1chieve study. *Prim Care Diabetes* 2014; 8: 111–117.
45. Mathieu C, Storms F, Tits J, *et al*. Switching from premixed insulin to basal–bolus insulin glargine plus rapid-acting insulin: The ATLANTIC study. *Acta Clin Belg* 2013; 68: 28–33.
46. Mosenzon O, Raz I. Intensification of insulin therapy for type 2 diabetic patients in primary care: Basal-bolus regimen versus premix insulin analogs: When and for whom? *Diabetes Care* 2013; 36(Supp_2): S212–S218.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Prisma checklist.

Data S2. Search strategy.

Figure S1. Sensitivity analysis by successively removing a particular study at a time to assess the influence of every single study on the pooled estimate for the mean difference in HbA1c, %, comparing premixed insulin versus basal-bolus regimen for type 2 diabetes.

Figure S2. Funnel plot along with Begg's and Egger's tests for the mean difference in HbA1c, %, in all 18 randomized controlled trials comparing premixed insulin versus basal-bolus regimen for type 2 diabetes.

Figure S3. Subgroup meta-analysis based on background diabetes therapy (patients who were already receiving insulin versus insulin naïve patients).

Figure S4. Subgroup meta-analysis based on background diabetes therapy (patients who were already receiving insulin versus insulin naïve patients).

Figure S5. Subgroup meta-analysis based on background diabetes therapy (patients who were already receiving insulin versus insulin naïve patients).

Figure S6. Subgroup meta-analysis based on background diabetes therapy (patients who were already receiving insulin versus insulin naïve patients).

Figure S7. Subgroup meta-analysis based on background diabetes therapy (patients who were already receiving insulin versus insulin naïve patients).

Table S1. The list of all identified records and studies excluded with reason during the process of full-text review.