REVIEW

Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: The purpose of this study was to compare insulin degludec with insulin glargine in terms of efficacy and safety in patients with type 2 diabetes.
Methods: We systematically searched PubMed, Embase, Web of Science, and Cochrane Library databases for randomized controlled trials

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published prior to 13 August 2018 (no language restrictions) which compared insulin degludec with insulin glargine. Our main endpoints were glycemic control, hypoglycemic event, weight gain, and serious adverse events (SAEs). We assessed pooled data using random-effects models.
Results: A total of 15 studies that included 9619 patients in the insulin degludec arm of the studies and 7075 patients in the insulin glargine arm were identified and subsequently assessed. Our analysis showed that compared with insulin glargine, insulin degludec yielded an improved mean reduction in fasting plasma glucose (FPG) (weighted mean difference [WMD] -5.20 mg/dL, 95% confidence interval [CI] -7.34, -3.07, $P < 0.00001$) and a lower ratio of participants experiencing ≥ 1 severe hypoglycemic event (relative risk [RR] 0.68, 95% CI 0.50, 0.93, $P = 0.01$) and nocturnal hypoglycemia (RR 0.81, 95% CI 0.75, 0.88, $P < 0.0001$); however, in the insulin degludec group there was a lower ratio of participants with glycated hemoglobin (HbA1c) of $\leq 7.0\%$ (RR 0.92, 95% CI 0.86, 0.98, $P = 0.01$). There was no statistically significant difference between the two treatment groups for HbA1c reduction (WMD 0.03, 95% CI -0.00, 0.07, $P = 0.08$), body weight gain (WMD 0.12, 95% CI -0.19, 0.43, $P = 0.46$), and proportion of participants with SAEs (RR 0.97, 95% CI 0.92, 1.02, $P = 0.20$).

Conclusions: Insulin degludec and insulin glargine provide similar glycemic control, but insulin degludec also lowers the risk of hypoglycemia. Consequently, insulin degludec may be an alternative treatment for the management of patients with type 2 diabetes who are prone to hypoglycemia with insulin glargine.

Keywords: Insulin degludec; Insulin glargine; Type 2 diabetes; Meta-analysis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by progressive deterioration of insulin-producing pancreatic beta cells, resulting in worsening hyperglycemia over time [1]. The typical clinical treatments for T2DM are the sequential addition of anti-diabetic drugs, basal insulin treatment, and more complex treatment regimens [2]. Basal-bolus regimens are usually the last option in this progression of treatments, but they fail to stop the loss of beta-cell function. In addition, even intensive basal-bolus insulin treatment is limited in terms of achieving glycemic targets due to insufficient insulin dose titration arising from concerns about the risks of severe hypoglycemia and serious adverse events (SAEs) [3]. Indeed, the ideal anti-diabetic treatment combines glycemic control and a low propensity for causing body weight gain and hypoglycemia.

Insulin glargine, the first-generation long-acting basal insulin analogue, has changed insulin treatments in T2DM. In earlier trials, insulin glargine showed a lower rate of nocturnal hypoglycemic episodes than did neutral protamine Hagedorn (NPH) insulins, with patients in both treatment groups showing equal weight gain and similar glycemic control [4]. However, compared with insulin degludec, insulin glargine has a shorter duration of action (18–26 h), and considerable residual variability still remains [5].

Insulin degludec is a novel ultra-long-acting basal insulin analogue that has been shown in developmental trials to have a duration of action of up to 42 h and a half-life of approximately 25 h [6]. The long-lasting effect of this insulin is primarily due to the formation of soluble polyhexamers at the injection site; the monomer is subsequently gradually separated and absorbed into the circulation, thereby producing stable pharmacokinetic profiles under the steady state condition [7]. In this context, strong physiological and clinical rationale lends support to the potential benefits of insulin degludec. First, with its longer duration of action, insulin degludec might enable the insulin dosage and number of insulin treatments to be reduced, which would encourage patients to optimize insulin treatment. Second, pharmacokinetic/pharmacodynamic (PK/PD) profiles of insulin degludec cause much less within-patient variability, resulting in lower risks of hypoglycemia [8]. The lower risk of severe hypoglycamia could decrease the risks of SAEs and mortality [9].

Given this compelling evidence, a series of clinical trials have assessed insulin degludec versus insulin glargine. Recognizing that individual studies might be unable on their own to provide sufficient data to affect real-life medical practice, we sought to objectively assess the potential role of insulin degludec treatment in the management of T2DM by compiling evidence from a number of studies. Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to establish the effect of insulin degludec versus insulin glargine on key outcomes in the treatment of patients with T2DM, including glycemic control, hypoglycamia, body weight gain, and SAEs.

METHODS

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [10]. The PRISMA checklist is included in Electronic Supplementary Material (ESM) Table S1.

Search Strategy

Our search strategy was to identify and retrieve all relevant studies published prior to 13 August 2018 from the PubMed, Embase, Web of

Science, and Cochrane Library databases. All related articles were retrieved without language or geographical limitations. The keywords used were "type 2 diabetes," "insulin degludec," and "insulin glargine." The reference lists of the relevant articles were also manually examined to identify other potentially related studies. The searches were conducted independently by two investigators (WCZ, JXT).

Eligibility Criteria

All studies included in the meta-analysis met the following inclusion criteria: (1) study design: RCTs; (2) patient population: patients with T2DM; (3) intervention: insulin degludec versus insulin glargine; (4) outcome variables: changes in glycated hemoglobin (HbA1c) or changes in laboratory-measured fasting plasma glucose (FPG) or proportion of participants with HbA1c $\leq 7.0\%$ OR proportion of participants experiencing ≥ 1 hypoglycemic event or changes in body weight or proportion of participants with major adverse cardiovascular events (MACEs), or proportion of participants with SAEs. The exclusion criteria were: (1) observational and retrospective studies; (2) duplicate publications; (3) letters, review articles; (4) cadaver subjects or animal studies; (5) studies in which the duration of the intervention was < 8 weeks.

Data Extraction and Quality Assessment

Two investigators (WCZ, JXT) independently reviewed the study titles and abstracts and extracted data from the articles. Disagreements were resolved by consensus and discussion with the corresponding authors (XDZ, HXC). The following study characteristics and results were extracted from each eligible study: (1) basic data (name of first author, publication year, location of study, study design; differential interventions; duration of interventions; total number of participants; age of participants; sex ratio; duration of diabetes; baseline HbA1c and FPG; baseline body mass index [BMI]; baseline body weight) and (2) outcomes (changes in HbA1c, FPG, and body weight [mean and standard deviation]; the number of participants with HbA1c $\leq 7.0\%$; the number of participants experiencing ≥ 1 hypoglycemic event; the number of participants with SAEs; the number of participants with MACEs). We did not contact the authors for additional data and only extracted the reported results from the published articles. Two independent reviewers (WCZ, JXT) rated risk for bias according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [11].

Statistical Analysis

We evaluated the efficacy and safety of insulin degludec versus insulin glargine on six outcomes: efficacy endpoints, as assessed by HbA1c, FPG, and proportion of participants with a target HbA1c of $\leq 7.0\%$ or lower; safety endpoints, as assessed by the incidence of confirmed hypoglycemia episodes (total, nocturnal, and severe); SAEs, and changes in body weight. We conducted meta-analyses using a random-effects model. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous variables (HbA1c, FPG, and body weight). We also calculated an overall relative risk (RR) and 95% CI to analyze the dichotomous data (proportion of participants with HbA1c $\leq 7.0\%$, proportion of participants experiencing ≥ 1 hypoglycemic event, and proportion of participants with SAEs). Statistical heterogeneity was checked by the Cochran Q test and I^2 tests. If heterogeneity was substantial ($P < 0.1$, $I^2 > 50\%$), a sensitivity analysis was performed to identify the source of the heterogeneity. If the heterogeneity could not be eliminated, we used a random-effects model. Publication bias was assessed using Egger's linear regression test, and we defined no publication bias as a P value of > 0.05. For all statistical analyses, a P value of < 0.05 was regarded as being indicative of statistical significance with the exception of heterogeneity. We conducted random-effects meta-regression to assess the impact of study characteristics on the effect sizes. The explanatory variables included sex ratio, age, baseline HbA1c, baseline BMI, baseline weight, baseline FPG, duration of

diabetes, and duration of interventions. Subgroup analyses were carried out based on background treatment (insulin-naïve or insulin treatment) and differential interventions of insulin degludec (once-daily or three times a week). We used RevMan version 5.3 software and StataSE version 12.0 statistical software (Stata Corp., College Station, TX, USA) for all statistical analyses.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Overall Characteristics of Selected Trials and Quality Assessment

We identified 1495 studies in our search of the databases, of which 15 (with data for 16,694 participants) were included in our analysis. These 15 RCTs were all published between 2012 and 2018. The flow diagram of the search procedure is shown in Fig. 1, and the characteristics of the included studies [12–25] are described in
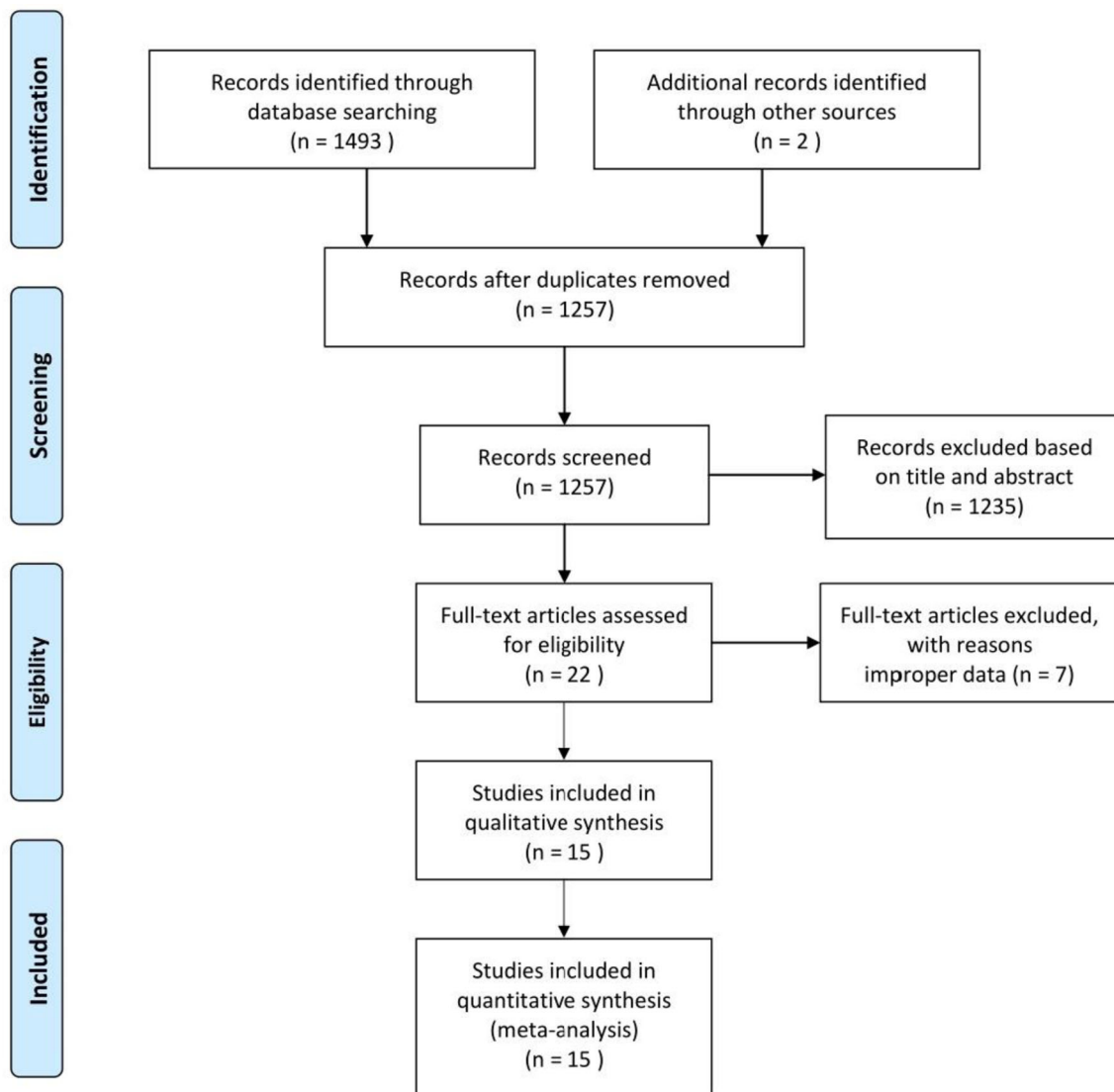

Fig. 1 Flow diagram for identifying eligible studies

Table 1 Baseline characteristics of randomized controlled trials included in the meta-analysis

First author	Year	Location	Design	Background treatment	Differential interventions	Duration of intervention (weeks)	Number of participants	Number of male participants	Mean age (years)	Mean baseline HbA1c (%)[a]	Mean baseline FPG (mg/dL)	Mean baseline BMI (kg/m²)	Mean baseline body weight (kg)	Mean duration of diabetes (years)
Rosenstock [21]	2018	158 sites in 16 countries	RCT	Insulin-naïve	IDeg-100[b] OD vs. IGlar-300[c] OD	24	929	502 (54%)	60.5	8.64 ± 0.82	186	31.5	89.7	10.6
Wysham [23]	2017	USA	Crossover RCT	Basal insulin ± OADs	IDeg-100 OD vs. IGlar-100[d] OD	32	720	382 (53.1%)	61.4	7.60	137	32.2	91.7	14.1
Aso [12]	2017	Japan	RCT	Insulin-naïve	IDeg OD vs. IGlar OD	24	44	20 (45.5%)	64.4	8.86	162.5	24.6	61.3	11.5
Marso [16]	2017	438 sites in 20 countries	RCT	Basal insulin ± OADs	IDeg-100 OD vs. IGlar-100 OD	96	7637	4778 (62.5%)	65	8.4 ± 1.7	171.7	33.6	96.1	16.4
Warren [22]	2017	USA	Crossover RCT	IGlar-100 OD	IDeg-200[e] OD vs. IGlar-100 OD	32	145	90 (62%)	55.3	8.15	144.5	36.2	105.2	12.1
Pan [19]	2016	68 sites in 6 countries	RCT	Insulin-naïve	IDeg-100 OD vs. IGlar-100 OD	26	833	433 (52%)	56	8.3	169.2	27.2	74.65	8
Hollander [15]	2015	123 sites in 12 countries	RCT	Basal insulin ± OADs	IDeg OD vs. IGlar OD	78	757	410 (54.2%)	58.7	8.25 ± 0.85	165.6	32.15	92.2	13.55
Onishi [18]	2013	52 sites in 6 countries	RCT	Insulin-naïve	IDeg-100 OD vs. IGlar-100 OD	26	435	233 (53.6%)	58.6	8.5 ± 0.8	153	25	65.7	11.6
Zinman [24]	2013	94 sites in 7 countries	RCT	Insulin-naïve	IDeg 3TWAM[f] vs. IGlar OD	26	459	261 (56.9%)	58.2	8.25 ± 0.85	170.4	32.45	93.3	8.85
Zinman [24]	2013	89 sites in7 countries	RCT	Insulin-naïve	IDeg 3TWPM[g] vs. IGlar OD	26	467	267 (57.2%)	57.4	8.3 ± 0.8	179	32.1	91.9	8.8
Rodbard [20]	2013	166 sites in 12 countries	RCT	Insulin-naïve	IDeg OD vs. IGlar OD	104	1030	648 (63%)	59	8.2 ± 0.8	173.7	31.25	90.6	9

Table 1 continued

First author	Year	Location	Design	Background treatment	Differential interventions	Duration of intervention (weeks)	Number of participants	Number of male participants	Mean age (years)	Mean baseline HbA$_{1c}$ (%)[a]	Mean baseline FPG (mg/dL)	Mean baseline BMI (kg/m^2)	Mean baseline body weight (kg)	Mean duration of diabetes (years)
Gough [14]	2013	106 sites in 8 countries	RCT	Insulin-naïve	IDeg-200 OD vs. IGlar-100 OD	26	457	243 (53.2%)	57.6	8.3 ± 0.95	173.2	32.4	92.5	8.2
Meneghini [17]	2013	69 sites in 14 countries	RCT	Basal insulin ± OADs	IDeg Flex vs. IDeg OD vs. IGlar OD	26	687	370 (54%)	56.4	8.4 ± 0.9	160.2	29.6	81.8	10.6
Zinman [25]	2012	166 sites in 12 countries	RCT	Insulin-naïve	IDeg-100 OD vs. IGlar-100 OD	52	1030	638 (61.9%)	59	8.2 ± 0.8	173.7	31.25	90.7	9
Garber [13]	2012	123 sites in 12 countries	RCT	Basal insulin ± OADs	IDeg-100 OD vs. IGlar-100 OD	52	992	538 (54%)	58.9	8.3 ± 0.8	165.6	32.1	92.4	13.5

BMI Body mass index, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *IDeg* insulin degludec, *IGlar* insulin glargine, *RCT* randomized clinical trial, *OD* once daily, *OADs* oral anti-diabetics drugs

[a] Data given as the mean ± standard deviation where available

[b] IDeg-100: the 100 U/mL formulation of insulin degludec

[c] IGlar-300: the 300 U/mL formulation of insulin glargine

[d] IGlar-100: the 100 U/mL formulation of insulin glargine

[e] IDeg-200: the 200 U/mL formulation of insulin degludec

[f] 3TWAM: IDeg was injected three times a week before breakfast

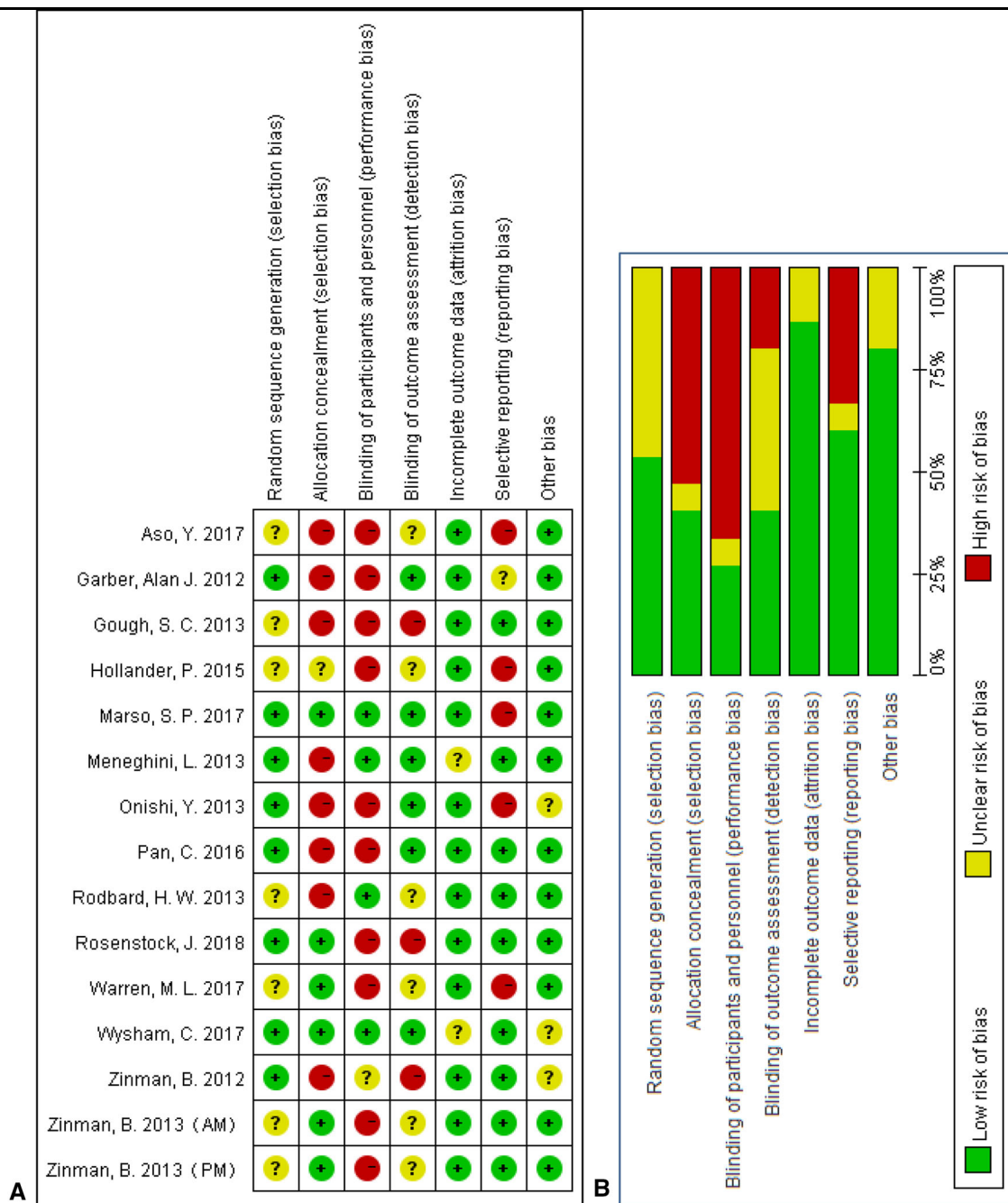[g] 3TWPM: IDeg was injected three times a week with the evening meal

Fig. 2 Assessment of risk of bias. **a** Summary of risk of bias presenting each risk of a bias item for each included study, **b** each risk of a bias item presented as a percentage across all 15 studies included in the analysis

Table 1. Mean trial duration was 43.3 (range 24–104) weeks. Patients had a mean baseline HbA1c of 8.31% (range 7.6–8.86%), mean baseline FPG of 165.7 (range 137–186) mg/dL, mean baseline BMI of 30.9 (range 24.6–36.2) kg/m^2, and mean duration of diabetes of 11.1 (range 8–16.4) years. Of the 15 RCTs, 12 were carried out in multiple countries [13–21, 24, 25], two in the USA [22, 23], and one in Japan [12]. In the two crossover trials, participants were switched directly to the other intervention without a washout period [22, 23]. Therefore, only the first treatment phrases were chosen in the meta-analysis, and we performed

a pre-specified sensitivity analysis for possible bias. Nine trials compared insulin degludec with insulin glargine on a background of insulin naïvety [12, 14, 18–21, 24, 25], leading us to perform a subgroup analysis based on the background treatment (insulin naïvety or insulin treatment). In 13 trials used Insulin degludec was administered once daily in 13 trials [12–23, 25] and three times per week in only two trials [24]. One of the RCTs was a three-arm trial (IDeg OD Flex vs. IDeg OD vs. IGlar OD) [17], where OD refers to once-daily administration, and OD Flex refers to intervals between injections ranging from 8 to 40 h. In accordance with the methods described in chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions [11], to analyze the three-aim study we combined the two groups IDeg OD Flex and IDeg OD and the compared the results of the merger with the IGlar OD group. Details of the risk of bias assessment are given in Fig. 2.

Glycemic Control

Ten studies (containing 11 trials) that included 7719 patients in the insulin degludec group and 6279 patients in the insulin glargine group reported the change in HbA1c between baseline and the end of the intervention. A random-effects model was used for this analysis ($P = 0.001$, $I^2 = 66.5\%$). A pooled analysis of all 11 trials revealed that insulin glargine led to a greater mean reduction in HbA1c than did insulin degludec (WMD 0.07, 95% CI 0.01, 0.13, $P = 0.019$; Fig. 3a), with statistically significant between-study heterogeneity ($P < 0.1$, $I^2 > 50\%$). In this analysis, no publication bias was evident ($P = 0.600$). In the subsequent sensitivity analysis, we excluded a study by Zinman et al. [24] and found that the I^2 value fell from 67 to 30%. Two parallel trials in this study were the only two trials in all of studies included in our meta-analysis to use insulin degludec three times a week. The sensitivity analysis comparing IDeg OD with IGlar OD (nine trials; 13,072 participants) showed a mean overall reduction in HbA1c in favor of insulin glargine, but the difference was not statistically significant (WMD 0.03, 95% CI − 0.01, 0.07, $P = 0.10$).

Fig. 3 Meta-analyses of insulin degludec versus insulin glargine, comparing changes in glycated hemoglobin (HbA1c) between baseline and end of intervention. Outcomes assessed are: **a** changes in HbA1c (%), **b** subgroup analysis comparing changes in HbA1c (%) between the insulin degludec (IDeg) OD group and the insulin glargine (IGlar) OD group based on the background treatment (insulin-naïve and insulin). *OD* Once daily ▶

Subgroup analysis ($P = 0.204$, $I^2 = 27\%$) based on the background treatment (insulin-naïve vs. insulin) was also performed to demonstrate that there was no statistically significant difference between the two treatment groups regarding changes in the HbA1c level (WMD 0.03, 95% CI − 0.00, 0.07, $P = 0.08$; Fig. 3b). We detected no significant between-study heterogeneity (Table 2).

Ten studies (containing 11 trials) that included 8031 patients in the insulin degludec group and 6223 patients in the insulin glargine group reported the changes in FPG between baseline and the end of the intervention. A random-effects model was used for this analysis ($P < 0.00001$, $I^2 = 76.3\%$,). A pooled analysis of 11 trials revealed that insulin degludec led to a greater mean reduction in FPG than did insulin glargine, but the difference was not statistically significant (WMD − 2.36, 95% CI − 6.51, 1.80, $P = 0.27$; Fig. 4a). In the subsequent sensitivity analysis, we excluded the study by Zinman et al. [24] and found that the I^2 value fell from 76 to 11%. The sensitivity analysis comparing IDeg OD with IGlar OD (nine trials; 13,328 participants) showed a mean overall reduction in FPG in favor of insulin degludec, with no significant between-study heterogeneity (WMD − 5.20, 95% CI − 7.34, − 3.07, $P < 0.00001$; Fig. 4b). There was no significant publication bias in this analysis ($P = 0.491$).

We also analyzed the proportion of participants with HbA1c ≤ 7.0% at the end of the intervention; these values were presented in ten trials that included 4105 patients in the insulin degludec group and 2459 patients in the insulin glargine group. A random-effect model was used for this analysis ($P = 0.12$, $I^2 = 37\%$). Insulin glargine was linked to a higher ratio of
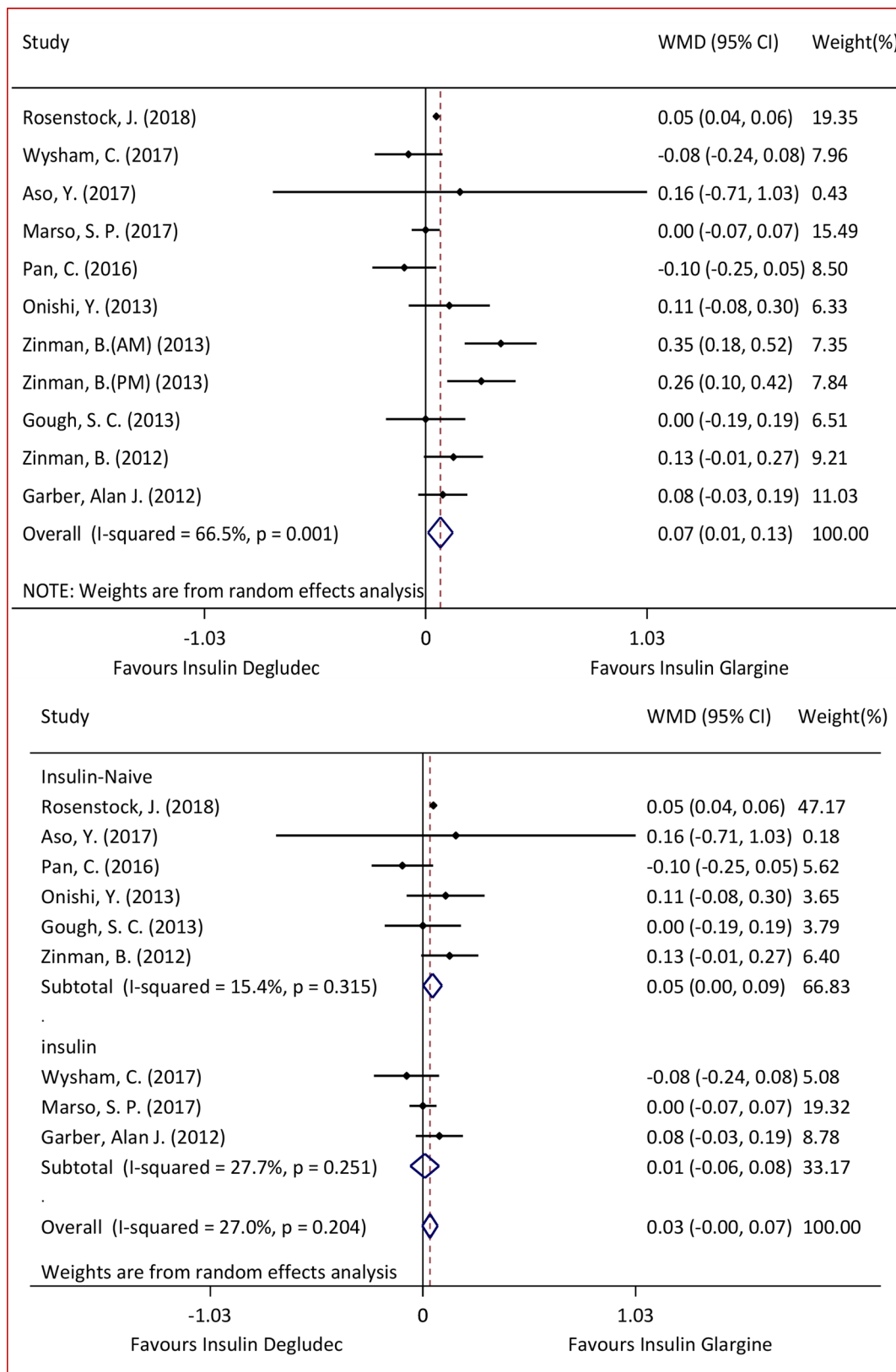
Study		WMD (95% CI)	Weight(%)
Rosenstock, J. (2018)		0.05 (0.04, 0.06)	19.35
Wysham, C. (2017)		-0.08 (-0.24, 0.08)	7.96
Aso, Y. (2017)		0.16 (-0.71, 1.03)	0.43
Marso, S. P. (2017)		0.00 (-0.07, 0.07)	15.49
Pan, C. (2016)		-0.10 (-0.25, 0.05)	8.50
Onishi, Y. (2013)		0.11 (-0.08, 0.30)	6.33
Zinman, B.(AM) (2013)		0.35 (0.18, 0.52)	7.35
Zinman, B.(PM) (2013)		0.26 (0.10, 0.42)	7.84
Gough, S. C. (2013)		0.00 (-0.19, 0.19)	6.51
Zinman, B. (2012)		0.13 (-0.01, 0.27)	9.21
Garber, Alan J. (2012)		0.08 (-0.03, 0.19)	11.03
Overall (I-squared = 66.5%, p = 0.001)		0.07 (0.01, 0.13)	100.00

NOTE: Weights are from random effects analysis

-1.03   0   1.03

Favours Insulin Degludec   Favours Insulin Glargine

Study		WMD (95% CI)	Weight(%)
Insulin-Naive			
Rosenstock, J. (2018)		0.05 (0.04, 0.06)	47.17
Aso, Y. (2017)		0.16 (-0.71, 1.03)	0.18
Pan, C. (2016)		-0.10 (-0.25, 0.05)	5.62
Onishi, Y. (2013)		0.11 (-0.08, 0.30)	3.65
Gough, S. C. (2013)		0.00 (-0.19, 0.19)	3.79
Zinman, B. (2012)		0.13 (-0.01, 0.27)	6.40
Subtotal (I-squared = 15.4%, p = 0.315)		0.05 (0.00, 0.09)	66.83
.			
insulin			
Wysham, C. (2017)		-0.08 (-0.24, 0.08)	5.08
Marso, S. P. (2017)		0.00 (-0.07, 0.07)	19.32
Garber, Alan J. (2012)		0.08 (-0.03, 0.19)	8.78
Subtotal (I-squared = 27.7%, p = 0.251)		0.01 (-0.06, 0.08)	33.17
.			
Overall (I-squared = 27.0%, p = 0.204)		0.03 (-0.00, 0.07)	100.00

Weights are from random effects analysis

-1.03   0   1.03

Favours Insulin Degludec   Favours Insulin Glargine

Table 2 Changes in glycated hemoglobin based on the background treatment

Changes in HbA1c	Trials (n)	Sample size		WMD	95% CI	P of χ^2	I^2 (%)	P for overall effect
		IDeg OD	IGlar OD					
Insulin-naïve	6	2335	1388	0.05	0.00, 0.09	0.32	15	0.049[a]
Insulin	3	4922	4427	0.01	− 0.06, 0.08	0.25	28	0.803
Total	9	7257	5815	0.03	− 0.00, 0.07	0.20	27	0.080

Means and standard deviations were used to assess the weighted mean difference, with respective 95% confidence intervals. A random-effects model was used in all analyses

CI Confidence interval, *WMD* weighted mean difference

[a] Value is statistically significant at the 95% confidence limit

participants with HbA1c $\leq$ 7.0% at the end of the study as compared to insulin degludec (RR 0.92 , 95% CI 0.86, 0.98, $P = 0.01$; ESM Fig. S1). The sensitivity analysis was performed by removing each study separately from the pooled analysis; however, between-study heterogeneity and consequence were not significantly influenced, thereby indicating the robustness of the results. In this analysis, no publication bias was evident ($P = 0.511$).

Hypoglycemic Events

Pooled analysis of the 12 studies (8903 participants; $P = 0.053$, $I^2 = 43.5\%$) that assessed the proportion of participants experiencing ≥ 1 hypoglycemic event showed a lower incidence of all confirmed hypoglycemic episodes when participants were treated with insulin degludec, as compared to treatment insulin glargine, but the difference was not statistically significant (RR 0.98, 95% CI 0.93, 1.03, $P = 0.43$; ESM Fig. S2). In this analysis, no publication bias was evident ($P = 0.769$).

Nine studies that included 8683 patients in the insulin degludec group and 6386 patients in the insulin glargine group reported the proportion of participants experiencing ≥ 1 severe hypoglycemic event. A random-effects model was applied for this analysis ($P = 0.175$, $I^2 = 30.5\%$). Insulin degludec was associated with a lower ratio of participants experiencing ≥ 1 severe hypoglycemic event as compared to insulin glargine (RR 0.68, 95% CI 0.50, 0.93, $P = 0.01$; Fig. 5a). The sensitivity analysis was

performed by removing each study from the pooled analysis; however, the between-study heterogeneity and consequence were not noticeably influenced by this procedure, which indicates the robustness of the results. In this analysis, no publication bias was evident ($P = 0.662$).

Thirteen studies that included 6293 patients in the insulin degludec group and 3633 patients in the insulin glargine group reported the proportion of participants experiencing ≥ 1 nocturnal hypoglycemic event. A random-effects model was applied for this analysis ($P = 0.491$, $I^2 = 0.0\%$). Insulin degludec was associated with a lower ratio of participants experiencing ≥ 1 nocturnal hypoglycemic event as compared to insulin glargine (RR 0.81, 95% CI 0.75, 0.88, $P < 0.0001$; Fig. 5b). In this analysis, no publication bias was evident ($P = 0.741$).

Body weight Control

Six studies that included 6713 patients in the insulin degludec group and 5431 patients in the insulin glargine group reported changes in body weight. A random-effect model was applied for this analysis ($P = 0.0003$, $I^2 = 79\%$). Pooling the data of these studies showed that insulin degludec led to a greater mean weight gain than did insulin glargine, but the difference was not statistically significant (WMD 0.23, 95% CI − 0.14, 0.61, $P = 0.22$; ESM Fig. S3Aa). In the subsequent sensitivity analysis, we excluded a study by Marso et al. [16] and found that the I^2 value fell from 79 to 37%, but again there was
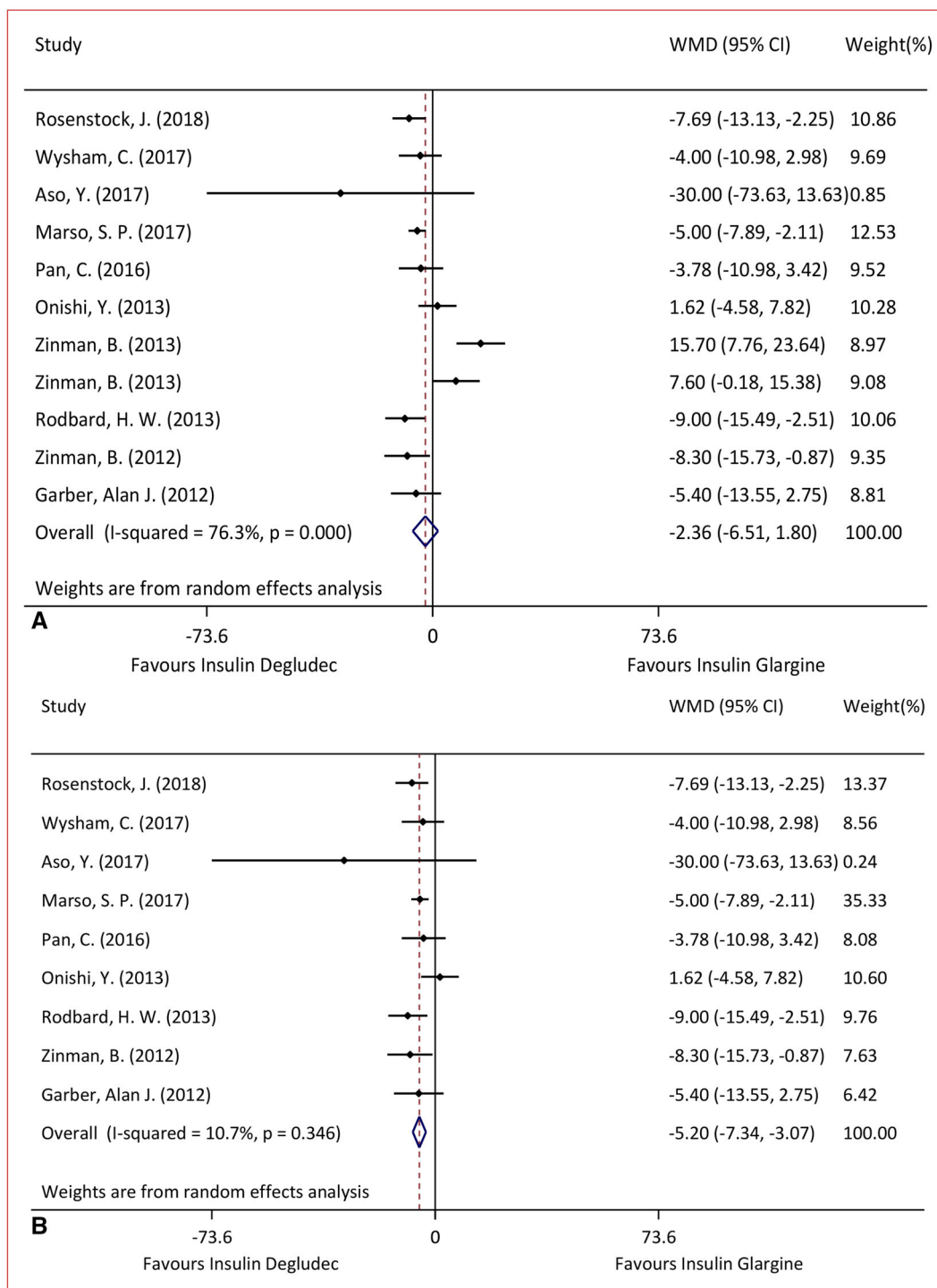
Fig. 4 Meta-analyses of IDeg versus IGlar, comparing changes in the fasting plasma glucose (FPG) level between baseline and end of intervention. Outcomes assessed are: **a** changes in FPG (mg/dL), **b** sensitivity analysis comparing changes in FPG between the IDeg OD group and IGlar OD group (study of Zinman et al. [24] excluded from the analysis)
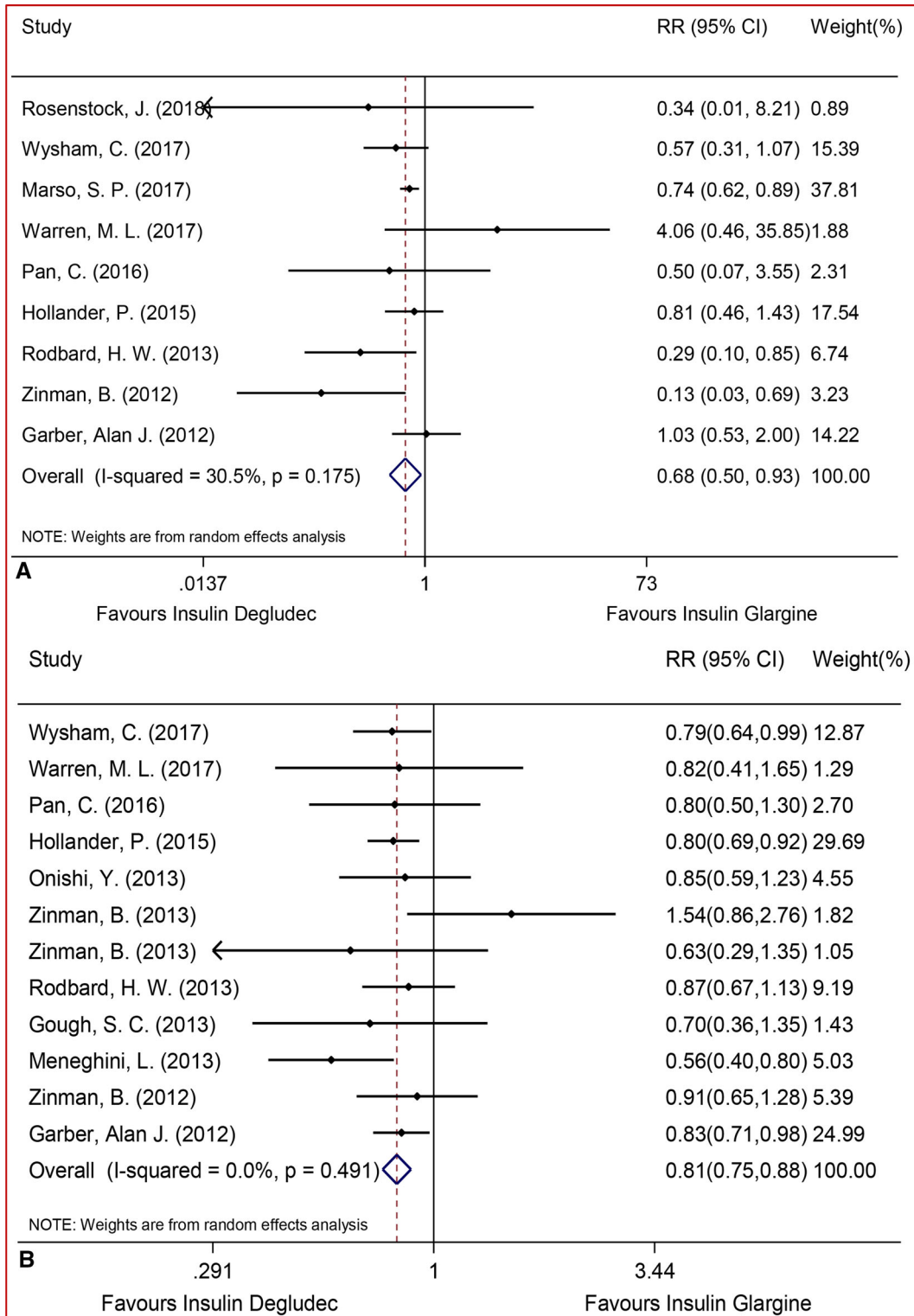
Fig. 5 Comparison of the proportion of participants experiencing ≥ 1 hypoglycemic event. Outcomes assessed are: **a** incidence of severe hypoglycemic episodes, **b** incidence of nocturnal hypoglycemic episodes. *RR* Relative risk

no statistically significant difference between the treatment groups (WMD 0.12, 95% CI − 0.19, 0.43, P = 0.46; ESM Fig. S3b).

Serious Adverse Events

Thirteen studies that included 9961 patients in the insulin degludec group and 7310 patients in the insulin glargine group reported the proportion of participants with SAEs. A random-effect model was applied for this analysis (P = 0.70, I^2= 0%). Insulin degludec was associated with a lower ratio of participants with SAEs as compared to insulin glargine, but the difference was not statistically significant (RR 0.97, 95% CI 0.92, 1.02, P = 0.20; ESM Fig. S4). In this analysis, no publication bias was evident (P = 0.367). Table 3 shows the main adverse events reported in the above-mentioned 13 studies.

Seven studies that included 6483 patients in the insulin degludec group and 5704 patients in the insulin glargine group reported the proportion of participants with MACEs. A random-effects model was applied to this analysis (P = 0.94, I^2= 0%). Insulin degludec was associated with a lower ratio of participants with MACEs as compared to insulin glargine. However, the difference was not statistically significant (RR 0.93, 95% CI 0.81, 1.07, P = 0.31; ESM Fig. S5). Table 3 shows the MACEs reported in the above-mentioned studies.

Sensitivity and Subgroup Analysis

Among all 11 studies that reported the changes in HbA1c, two trials by Zinman et al. [24] were the only two studies to use insulin degludec three times a week. In the sensitivity analysis, we excluded these two trials and found that the I^2 value fell from 67 to 30%. Additionally, when these two trials were excluded from all 11 studies that reported the changes in FPG, the I^2 value fell from 76 to 11%. The sensitivity analysis on changes in body weight was performed without the source of heterogeneity (ESM Fig. S6). In all six studies that reported changes in body weight, one study with a large sample size by Marso et al. [16] showed a significant

difference in changes in body weight between the two treatment groups. By excluding this study, we found that the I^2 value fell from 79 to 37%. Based on the background treatment (insulin-naïve or insulin), a subgroup analysis was also performed to compare the changes in HbA1c between the IDeg OD group and IGlar OD group; no significant between-study heterogeneity was detected (Table 2).

Meta-regression

In the context of comparing the efficacy and safety of insulin degludec and insulin glargine, we performed meta-regression on ten studies comparing the changes in HbA1c, on ten studies comparing the changes in FPG, on nine studies comparing the proportion of participants with HbA1c ≤ 7.0%, on 11 studies comparing the proportion of participants with confirmed hypoglycemia, on nine studies comparing the proportion of participants with severe hypoglycemia, on 12 studies comparing the proportion of participants with nocturnal hypoglycemia, and on 12 studies comparing the proportion of participants with SAEs. Our results showed that sex ratio, mean age, baseline HbA1c, baseline BMI, baseline weight, baseline FPG, duration of diabetes, and duration of interventions had no significant impact (P > 0.05) on the effect size of the differences of these outcomes in patients with T2DM (ESM Table S2).

DISCUSSION

The first long-acting basal insulin analogue, insulin glargine, is associated with lower rates of hypoglycemic episodes and less day-to-day variability than NPH insulins. However, because it fails to offer reliable full-day coverage, considerable residual variability and hypoglycemia risk still remain [4, 5]. Insulin degludec, a novel ultra-long-acting basal insulin analogue with a duration of action of > 40 h and a half-life of approximately 25 h, has flatter action profiles and a longer duration of action than insulin glargine [6, 8]. However, the very long action of insulin degludec may cause insulin adjustments

Table 3 Main adverse events reported

Adverse event	Studies (n)	Insulin degludec			Insulin glargine			RR	95% CI	P of χ²	I² (%)	P for overall effect
		Sample size	Reported cases (n)	Incidence rate (%)	Sample size	Reported cases (n)	Incidence rate (%)					
Adjudicated MACE	7	6483	376	5.80	5704	383	6.71	0.930	0.811, 1.068	0.935	0.00	0.305
Myocardial infarction	3	5242	157	3.00	4735	176	3.72	0.862	0.697, 1.065	0.858	0.0	0.168
Unstable angina pectoris	3	5242	80	1.53	4735	81	1.71	0.924	0.678, 1.259	0.422	0.0	0.615
Acute coronary syndrome	3	1213	20	1.65	714	10	1.40	0.892	0.406, 1.957	0.882	0.0	0.775
Nonfatal stroke	4	5469	83	1.52	4964	81	1.63	0.952	0.699, 1.297	0.445	0.0	0.756
Most frequent adverse events (≥ 5%)												
Headaches	2	994	52	5.23	485	33	6.80	0.954	0.611, 1.489	0.444	0.0	0.836
Nasopharyngitis	3	1278	86	6.73	631	50	7.92	0.863	0.579, 1.286	0.253	27.3	0.468
Upper respiratory tract infection	3	1278	60	4.69	631	56	8.87	0.518	0.362, 0.741	0.964	0.0	0.000[a]
Diarrhea	2	994	41	4.12	485	29	5.98	0.855	0.532, 1.374	0.829	0.0	0.518
Deaths	3	5255	209	3.98	4741	230	4.85	0.814	0.544, 1.219	0.318	12.7	0.318
Cardiovascular death	3	5242	143	2.73	4735	144	3.04	0.970	0.772, 1.220	0.742	0.0	0.797

Means and standard deviations were used to assess the WMD, with respective 95% confidence intervals. Random-effects models were used in all analyses

MACE Major adverse cardiovascular event, RR relative risk

[a] Value is statistically significant at the 95% confidence limit

to be delayed as well as insulin stacking, especially when extra dosages are required by patients with T2DM, which may increase the risk of hypoglycemia. Therefore, numerous trials have focused on determining whether insulin degludec has better clinical efficacy and safety than insulin glargine.

Our pooled results showed that insulin glargine provided greater HbA1c reduction than insulin degludec, but with statistically significant between-study heterogeneity. In a subsequent sensitivity analysis, we excluded two trials that used insulin degludec three times a week [24] and found that there was no statistical difference for the HbA1c reduction without statistically significant between-study heterogeneity, which suggests that the efficacy of the two treatment groups is related to dosing regimens (once-daily vs. three times a week). Subgroup analysis based on the background treatment (insulin-naïve or insulin) was also conducted to show that there was no statistically significant difference in HbA1c reduction. Furthermore, insulin glargine was associated with a higher ratio of participants with an HbA1c of ≤ 7.0% at the end of the study as compared to insulin degludec. Additionally, our results show that IGlar OD led to a lower reduction in FPG than did IDeg OD, with no significant between-study heterogeneity. In short, these results suggest that insulin glargine may provide a similar glycemic control as insulin degludec.

Indeed, in the management of T2DM, the ideal triumvirate of short-term outcomes includes not only a potent glucose-lowering capacity, but also a low propensity for causing hypoglycemia and body weight gain [26]. Compared with insulin glargine, insulin degludec is associated with a lower ratio of participants experiencing ≥ 1 severe hypoglycemic event, which is notably related to its lower variability of daily fasting glycemia [27]. In our meta-analysis, we found that insulin degludec reduced the incidence of nocturnal hypoglycemic events as compared to insulin glargine, an action which is correlated with its PK/PD profiles: insulin degludec has flatter action profiles and longer duration of action than insulin glargine. It is generally known that

nocturnal hypoglycemia, especially severe hypoglycemia, increases the risk of mortality, cardiovascular events, and SAEs; this causes widespread concern among patients, resulting in T2DM patients being reluctant to optimize insulin treatment [9]. Insulin degludec can notably reduce the risk of nocturnal and severe hypoglycemia; as such, it represents an advance in the management of hypoglycemic events in patients with T2DM [6, 8]. There was no statistical difference in body weight gain between the two treatment groups in the trials included in our meta-analysis, but more studies with larger sample sizes should be performed to determine changes in body weight. In the trials included in our meta-analysis, the ratio of patients with SAEs was lower in the insulin degludec group than in the insulin glargine group, but the difference was not statistically different. This result could be explained by the possibility that the criteria used for the definition of SAEs in the different trials were not fully consistent.

There are several strengths to our meta-analysis. First, the findings of our study are robust and consistent, since the sources of heterogeneity in our meta-analysis were determined and no significant between-study heterogeneity was detected in the additional sensitivity analysis. Indeed, this consistency is apparent despite the RCTs included in the meta-analysis differing in terms of background therapy and dosing regimens, and is proved by the subgroup analyses. Second, a large number of RCTs and patients with T2DM are included in our meta-analysis, which improved the statistical power of the meta-analysis on rare outcomes, such as the proportion of participants experiencing ≥ 1 severe hypoglycemic event, MACEs, and SAEs. Finally, two reviewers conducted comprehensive literature searches and quality assessments independently of each other, which minimizes the risk of bias and makes the results more reliable.

A limitation of this analysis is that while most of the included studies have been published in high-impact journals, there were several study characteristics that pose potential risks of bias, such as open-label design and manufacturer funding. Second, differences in insulin preparations, including medication

frequency (once-daily or three times a week), drug concentration (100 U/mL, 200 U/mL, or 300 U/mL), and intervals between injections, may cause between-study heterogeneity. Third, the criteria used for the definition of severe hypoglycemia and SAEs in the different trials may not be fully consistent. Finally, the difference in costs between these two insulins was not taken into account in this analysis. However, cost is always a factor that is taken into consideration when clinicians are prescribing diabetic patients; therefore, future researchers should pay attention to this issue.

CONCLUSIONS

Findings from our meta-analysis show that insulin degludec has an overall beneficial effect on the management of type 2 diabetes as compared to insulin glargine, mainly manifesting in the lower risks of severe and nocturnal hypoglycemia.

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REFERENCES

1. Kahn SE, Zraika S, Utzschneider KM, Hull RL. The beta cell lesion in type 2 diabetes: there has to be a primary functional abnormality. Diabetologia. 2009;52(6):1003–12.

2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364–79.

3. Wajchenberg BL. Beta-cell failure in diabetes and preservation by clinical treatment. Endocr Rev. 2007;28(2):187–218.

4. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26(11):3080–6.

5. Pettus J, Santos Cavaiola T, Tamborlane WV, Edelman S. The past, present, and future of basal insulins. Diabetes Metab Res Rev. 2016;32(6):478–96.

6. Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab. 2012;14(10):944–50.

7. Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharm Res. 2012;29(8):2104–14.

8. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab. 2012;14(9):859–64.

9. Pieber TR, Marso SP, McGuire DK, et al. DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality. Diabetologia. 2018;61(1):58–65.

10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.

11. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

12. Aso Y, Suzuki K, Chiba Y, et al. Effect of insulin degludec versus insulin glargine on glycemic control and daily fasting blood glucose variability in insulin-naive Japanese patients with type 2 diabetes: I'D GOT trial. Diabetes Res Clin Pract. 2017;130:237–43.

13. Garber AJ, King AB, Prato SD, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379(9825):1498–507.

14. Gough SC, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. Diabetes Care. 2013;36(9):2536–42.

15. Hollander P, King AB, Del Prato S, et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. Diabetes Obes Metab. 2015;17(2):202–6.

16. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017;377(8):723–32.

17. Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care. 2013;36(4):858–64.

18. Onishi Y, Iwamoto Y, Yoo SJ, et al. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Investig. 2013;4(6):605–12.

19. Pan C, Gross JL, Yang W, et al. A multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naive patients with type 2 diabetes mellitus. Drugs R D. 2016;16(2):239–49.

20. Rodbard HW, Cariou B, Zinman B, et al. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabet Med. 2013;30(11):1298–304.

21. Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 Units/mL versus insulin degludec 100 Units/mL in insulin-naive type 2 diabetes: the randomized head-to-head BRIGHT trial. Diabetes Care. 2018;41(10):2147–54.

22. Warren ML, Chaykin LB, Jabbour S, et al. Insulin degludec 200 units/mL Is associated with lower injection frequency and improved patient-reported outcomes compared with insulin glargine 100 Units/mL in patients with type 2 diabetes requiring high-dose insulin. Clin Diabetes. 2017;35(2):90–5.

23. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA. 2017;318(1):45–56.

24. Zinman B, DeVries JH, Bode B, et al. Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naive patients with type 2 diabetes: results of two phase 3, 26 week, randomised, open-label, treat-to-target, non-inferiority trials. Lancet Diabetes Endocrinol. 2013;1(2):123–31.

25. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012;35(12):2464–71.

26. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384(9961): 2228–34.

27. Zinman B, Marso SP, Poulter NR, et al. Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2). Diabetologia. 2018;61(1):48–57.