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Comparison of daily insulin dose and other anti-diabetic medications usage for type 2 diabetes patients treated with an analog basal insulin Systematic review and Single arm Meta-Analysis.

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Abstract

Background: Type 2 diabetes (T2D) is a chronic developing illness that accounts for over 90% of all people with diabetes.

Aim: To evaluate the daily insulin dosage and the utilization of additional anti-diabetic drugs in cases with type 2 diabetes receiving analog basal insulin therapy.

Patients and methods: This systematic review and single-arm meta-analysis aimed to evaluate the use of analog basal insulin in cases with T2D. The study included data from four primary research articles, conducted in various geographic locations such as Denmark, the USA, and multicenter sites spanning 80 countries. The study design adhered to the PRISMA guidelines for systematic reviews, ensuring a rigorous and transparent approach.

Results: No variation has been observed in the continuing of any non-insulin anti-diabetic medicines among cases receiving insulin detemir (DET) and those receiving insulin glargine (GLAR). Most cases utilizing metformin, sulfonylureas, thiazolidinediones, or exenatide prior to the start of insulin detemir or insulin glargine maintained the same class of medicine following the introduction of insulin. With RR and 95% CI; 0.57[0.51, 0.64] for metformin, 0.078[0.047, 0.1] for DPP-4 inhibitors, 0.1[0.02, 0.34] for sulfonylureas and 0.11[0.008, 0.2] for TZD. From figure 3 to figure 6 represents Forest plots for this outcome.

Conclusion: The study found no difference in non-insulin anti-diabetic agent continuation among DET and GLAR cases, with metformin being the most common concomitant medication.

Key words: T2D; Insulin Dose; DET.

Introduction

Type 2 diabetes (T2D) is a chronic, progressive condition that constitutes roughly ninety percent of all diabetes cases. The American Diabetes Association (ADA) endorses metformin as the primary pharmacological intervention; however, other treatments, such as oral diabetes drugs (OADs), glucagon-like peptide-1 receptor agonists (GLP-1 RA), or insulin, are frequently needed to attain sufficient glycemic regulation.**(1)** A consensus investigation conducted by the ADA and the EASD advocates for basal insulin as the optimum initial insulin formulation for cases with T2D with glycated hemoglobin over nine percent, despite optimal oral antidiabetic treatment. **(2); (3)**

Basal insulin primarily reduces fasting plasma glucose (FPG); however, over time, postprandial hyperglycemia contributes significantly to an elevated HbA1c. In such patients, more complex insulin regimens such as mealtime rapid-acting insulin plus basal insulin or premixed insulin

are used to target FPG and postprandial glucose (PPG) to achieve optimal glycaemic control **(4).**

Maintaining optimal glucose control is crucial for diabetic cases to prevent the onset of complications. Insulin therapy for type 2 diabetes could be required to attain target blood glucose levels if oral antihyperglycemic agents (AHAs) are inadequate, according to the European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) statement. Basal-bolus insulin regimens mimic the physiological sequence of insulin secretion & yield a more stable 24-hour glucose profile than standard insulin regimens. Nonetheless, these regimens may provoke hyperinsulinemia, thereby expediting atherosclerosis & heightening the possibility of hypoglycemia. **(5)**

Effective glycemic control is crucial for preventing diabetes-related complications in cases with type 2 diabetes, such as cardiovascular disease, cerebrovascular accidents, hypertension, visual impairment, renal illness, neuropathy, and amputations. To achieve glycemic control (e.g. HbA1c <7.5%), individuals with Type 2 Diabetes benefit from interventions aimed at enhancing insulin sensitivity, including dietary and activity modifications. **(6)**

Insulin may be administered alongside oral antidiabetic agents or GLP-1 analogues and can be utilized in either a basal-only or a basal-bolus regimen. The presently accessible basal insulin formulations comprise two long-acting insulin analogs—insulin detemir and GLAR—alongside the intermediate-acting human insulin, neutral protamine Hagedorn (NPH) insulin. **(7)**

Our meta-analysis and systematic review encompassed Four studies, including 19985 cases approximately. Our included studies' geographic distributions are Denmark, USA. Bajaj et al., and Mathieu et al., were multicenter studies. Mathieu et al., was Multicenter across 80 countries.

This investigation aimed to examine the daily insulin dosage and the utilization of other antidiabetic drugs in individuals with type 2 diabetes receiving analog basal insulin therapy.

Patients and methods

This systematic review and single-arm meta-analysis aimed to evaluate the use of analog basal insulin in cases with T2D. The study included data from four primary research articles, conducted in various geographic locations such as Denmark, the USA, and multicenter sites spanning 80 countries. The study design adhered to the PRISMA guidelines for systematic reviews, ensuring a rigorous and transparent approach.

Inclusion Criteria: Adults (≥18 years) diagnosed with T2D ,cases received analog basal insulin, including insulin detemir (DET), insulin glargine (GLAR), or insulin icodec and glycated hemoglobin (HbA1c) levels >9% despite maximal oral anti-diabetic therapy ,availability of detailed data on daily insulin consumption ,concurrent use of non-insulin glucose-lowering medications and studies published in peer-reviewed journals with well-documented methodologies and follow-up periods.

Exclusion Criteria: Patients diagnosed with type 1 diabetes or other non-T2D forms of diabetes, pregnant or breastfeeding women, individuals with severe comorbid conditions or contraindications to insulin therapy and studies with insufficient data reporting, high risk of bias, or inconsistent methodologies.

Patient Population

The meta-analysis encompassed data from approximately 19,985 patients, with baseline demographics extracted from the included studies. These patients had longstanding T2D and were inadequately controlled on previous oral anti-diabetic treatment, necessitating the initiation of basal insulin treatment.

Data Collection and Variables

Data were collected systematically from the included studies, focusing on:Patient demographics (age, gender) ,baseline HbA1c levels and glycemic control metrics ,daily insulin consumption (DACON) and type of basal insulin used (DET vs. GLAR vs. icodec) and concurrent use of non-insulin glucose-lowering medications, including metformin, sulfonylureas (SUs), DPP-4 inhibitors, and TZDs.

Literature Search and Screening

A comprehensive search across four electronic databases yielded 506 studies initially. After removing duplicates, 202 studies underwent abstract and title screening. Of these, 12 were reviewed in full, and four met the inclusion criteria for the meta-analysis. The PRISMA flowchart (Figure one) outlines the study selection process.

Risk of Bias Evaluation

The quality of the research involved has been evaluated using the ROB1 tool. Studies were rated based on domains such as selection, detection, and performance biases. Two of the research involved have been rated as having a high probability of detection and performance bias.

Statistical Analysis

Meta-analysis techniques were applied to pool the data: Risk ratios (RR) with ninety-five percent confidence intervals (CI) were calculated for categorical outcomes, such as continuation of non-insulin medications. Mean differences (MD) were computed for continuous variables, such as daily insulin consumption. Heterogeneity across studies was assessed using Chi-squared tests (Chi-p) and I^2 statistics. A significant level of heterogeneity was observed, with I^2 reaching 97%.

Results

3.1. Literature search results:

During an initial exploration of four databases, we discovered 506 research studies. After eliminating duplicate studies, 202 unique publications are subjected to further assessment. The screening method involved titles and abstracts, resulting in the selection of twelve publications for thorough full-text analysis. Ultimately, four studies conformed to the specified inclusion criteria. The PRISMA flowchart in **Figure 1** illustrates the selection process visually.

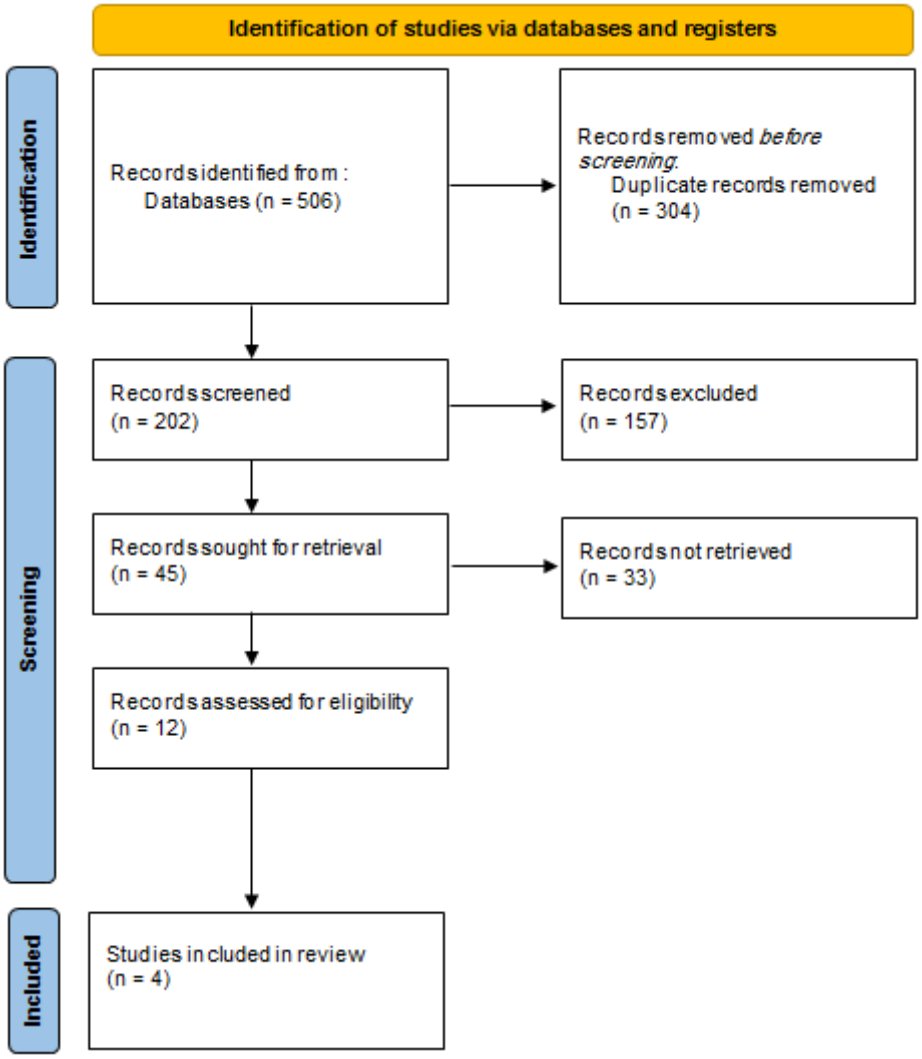

Figure 1: PRISMA flow chart for research selection process.

3.2. Characteristics of the included studies: Our systematic review and meta-analysis involved Four research, involving 19985 cases roughly. Our included studies' geographic distributions are Denmark, USA. Bajaj et al., and Mathieu et al., were multicenter studies. Mathieu et al., was Multicenter across 80 countries. The features and baseline summary of the research involved are presented in Table 1.

Table 1: Summary of Characteristic of Involved Studies.

Study ID	Study Design	Site	Sample size	Sample size	Insulin type	Age	Female
Bajaj. (8)	Multicenter, open-label RCT	Multicenter UK,Italy and Denmark	104	54	Insulin Icodec	62.4 ± 7.2	39 (72.2)M
				50	Insulin Glargine	60.5 ± 7.9	33 (66.0)
Jakobsen (6)	Cross Sectional	Denmark	536	251	Detemir	61	101
				285	Glargine	60	130
Junhua. (9)	Case-control	USA	18,763	2215 (11.8%)	detemir (DET)	56.9 (18.1)	47.30%
				16,548 (88.2%)	glargine (GLAR)		
Mathieu. (10)	open-label, multicentre RCT	Multicenter across 80 countries	582	(291	Insulin icodec	59.7	137
				(291	insulin glargine	59.9	141

3.3. Risk of bias evaluation:

Most of our involved studies had moderate Quality, ROB1 tool showed that both Bajaj et al., and Mathieu et al., studies had high risk of bias regarding detection and performance bias domains. Risk of bias assessment table and graph are provided in Table 1& Figure 2.

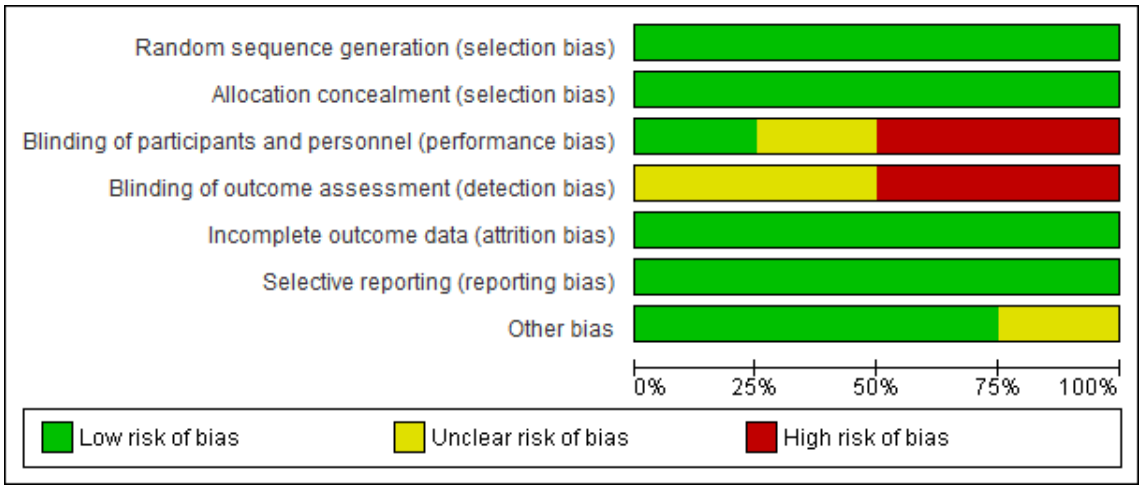

Figure 2: Risk of bias graph.

Table 2: risk of bias summary.

4. Outcomes:

Concomitant non-insulin glucose-lowering medications at screening:

No distinction has been observed in the continuation of any non-insulin anti-diabetic medicines among cases receiving DET and those receiving GLAR. Most cases utilizing metformin, sulfonylureas, thiazolidinediones, or exenatide before commencing insulin detemir or insulin glargine persisted in the same class of medicine following the initiation of insulin. With RR

and 95% CI; 0.57[0.51, 0.64] for metformin, 0.078[0.047, 0.1] for DPP-4 inhibitors, 0.1[0.02, 0.34] for sulfonylureas and 0.11[0.008, 0.2] for TZD. From figure 3 to figure 6 represents Forest plots for this outcome.

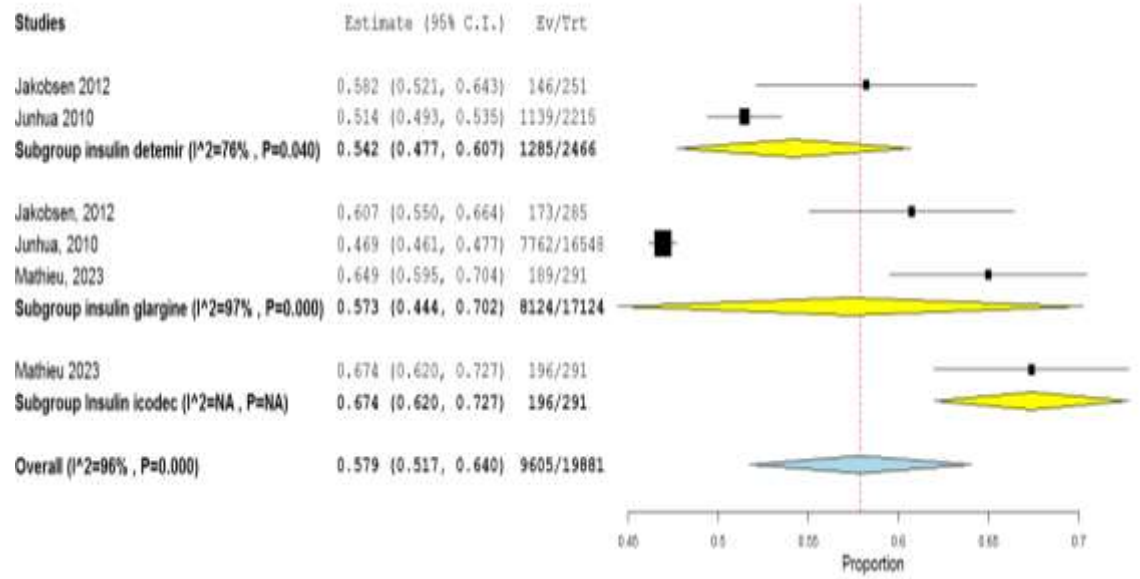

Figure 3: forest plot for patients Concomitantly using metformin with an analog basal insulin at screening.

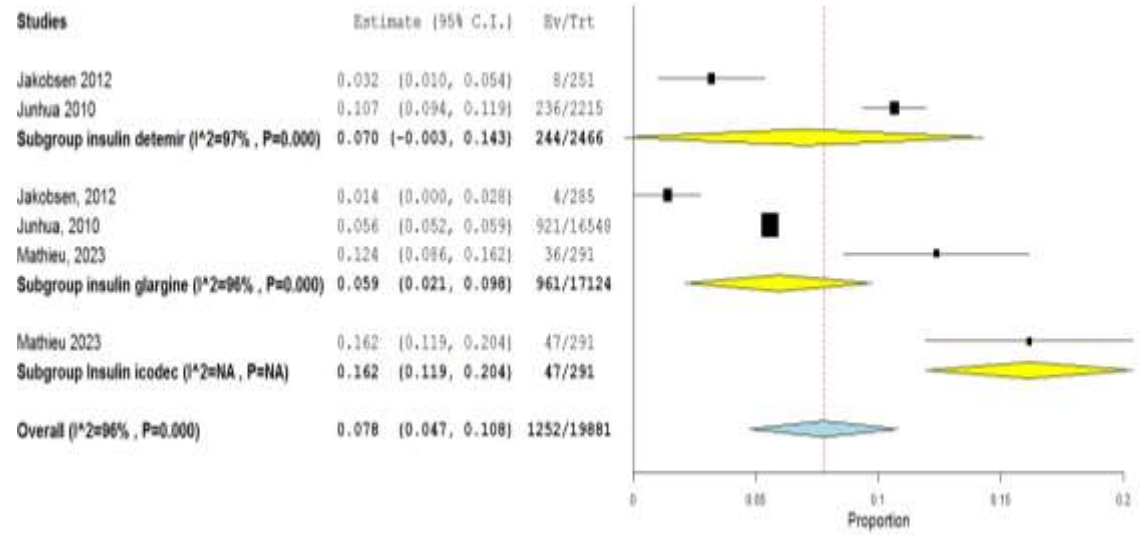

Figure 4: forest plot for patients Concomitantly using DPP-4 inhibitors with an analog basal insulin at screening.

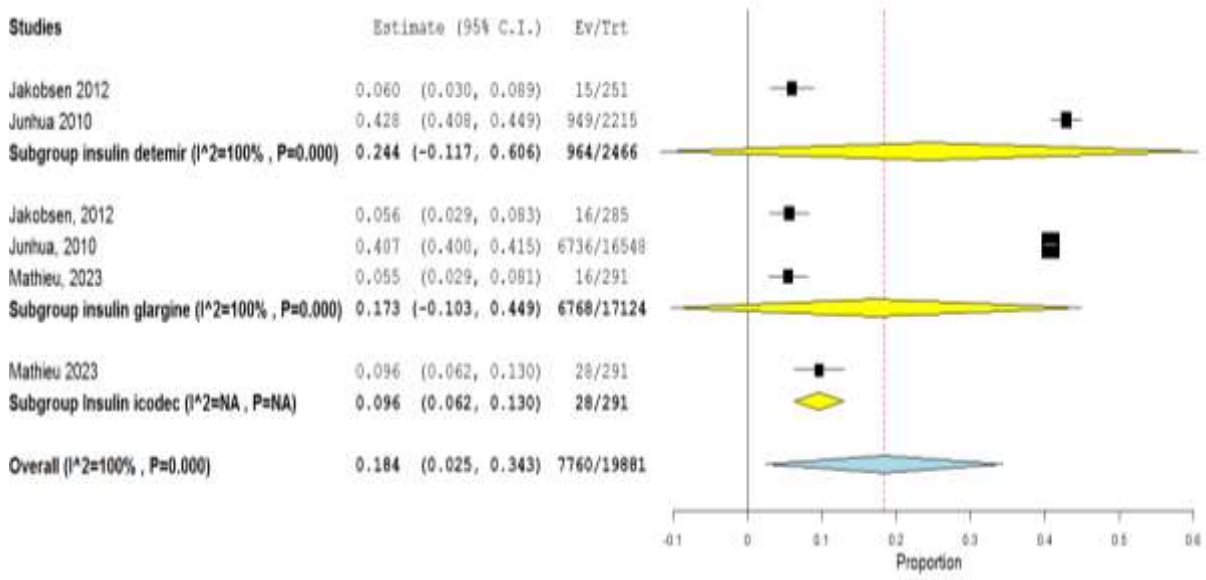

Figure 5: forest plot for patients Concomitantly using Sulfonylureas with an analog basal insulin at screening.

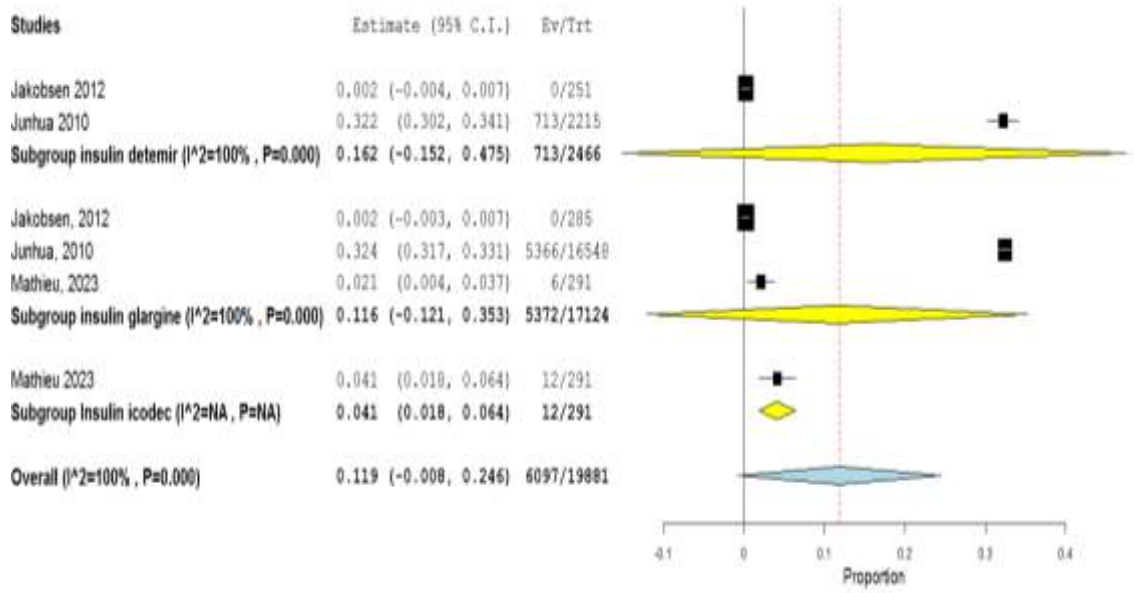

Figure 6: forest plot for patients Concomitantly using TZD with an analog basal insulin at screening.
insulin glargine

Mean (median) DACON daily average consumption:
Mean daily insulin consumption didn't significantly differ overall units for insulin detemir versus units for insulin glargine; our pooled MDs with 95% CI was 41.3[37.16, 45.6], major heterogenity was detected among our pooled studies with chi-p 0.0001 and I^2 97%. **Figure 7:** represents the forest plot for DACON of insulin DET and GLAR.

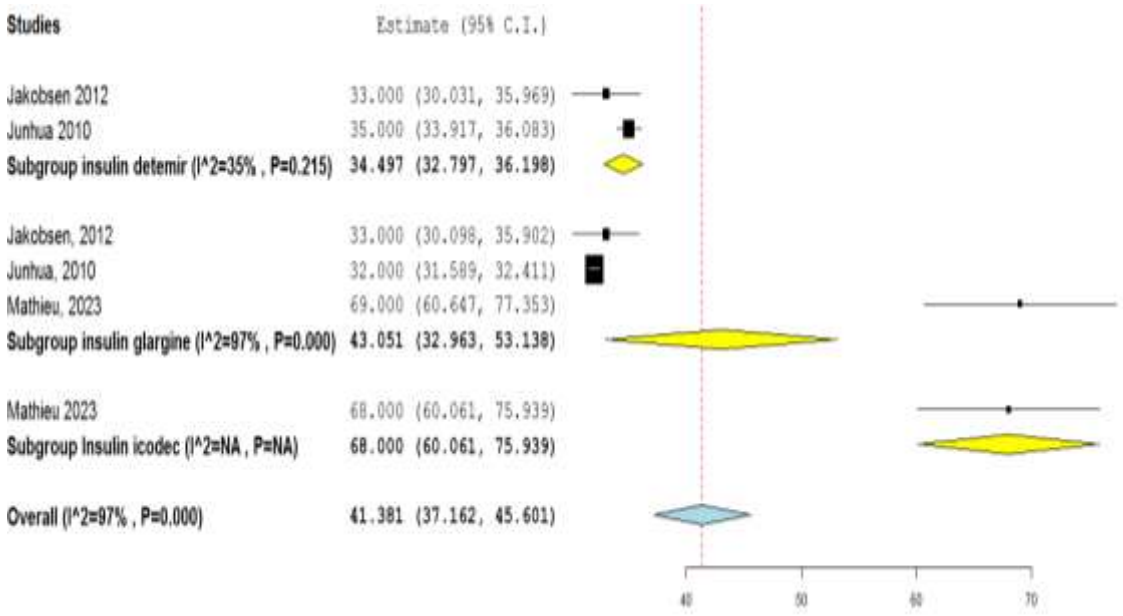

Figure 7: Forest plot for DACON of insulin DET and GLAR.

Discussion

Risk of bias evaluation: Most of our involved studies had moderate Quality, ROB1 tool showed that both Bajaj et al., and Mathieu et al., studies had high risk of bias regarding detection and performance bias domains. **(6) , (8), (9), (10)**

Regarding concomitant non-insulin glucose-lowering medications at screening

Our meta-analysis indicated no distinction in the continuing of any non-insulin anti-diabetic medicines among cases receiving insulin detemir and those receiving insulin glargine. Most cases utilizing metformin, sulfonylureas, thiazolidinediones, or exenatide before commencing insulin detemir or insulin glargine persisted in the same class of medicine following the initiation of insulin. With RR and 95% CI; 0.57[0.51, 0.64] for metformin, 0.078[0.047, 0.1] for DPP-4 inhibitors, 0.1[0.02, 0.34] for sulfonylureas and 0.11[0.008, 0.2] for TZD.

Jakobsen et al. (6) aimed to compare the real-life daily dosages of DET and GLAR in cases with T2D when given one time every day. They stated significant or borderline significant variations in concomitant insulin utilize, with a greater number of insulin detemir cases received Actrapid and more insulin glargine cases receiving with Insuman Rapid. Nevertheless, the proportion of T2D cases in the research group receiving these treatments was minimal, and it remains uncertain whether similar disparities are present among T2D cases generally.

McAdam et al. (9) investigated the insulin consumption in a significant group of T2D cases treated with either DET or GLAR in a real-world context, accounting for the application of additional antidiabetic agents. They found insignificant distinction in the continuation of any non-insulin antidiabetic agents among the insulin detemir and insulin glargine groups, with metformin being the predominant concomitant glucose-lowering medication, then sulfonylureas.

Mathieu et al. (10) aimed to evaluate the safety and efficacy of once-weekly icodec in comparison to once-daily insulin glargine U100 in cases with long-standing T2D on a basal-bolus regimen. They showed statistically insignificant differences among the groups being examined concerning concomitant non-insulin glucose-lowering medications as well as identified that the most prevalent basal insulins at screening for the two therapies were glargine U100, insulin degludec, and insulin glargine U300. Metformin, SGLT-2 inhibitors, and DPP-4 inhibitors were the predominant concurrent glucose-lowering agents and types of medication.

Regarding mean (median) DACON daily average consumption:
Our metanalysis showed that daily insulin consumption didn't significantly differ overall units for insulin detemir versus units for insulin glargine; our pooled MDs with 95% CI was 41.3[37.16, 45.6], major heterogenity was detected among our pooled studies with chi-p 0.0001 and I^2 97%.
McAdam et al. (9) discovered that no difference in daily insulin consumption has been seen among insulin detemir and insulin glargine in the unmatched analysis, wherein insulin detemir cases a greater number of classes of antidiabetic medications applied before the start of the basal analog compared to insulin glargine cases.
Jakobsen et al. (6) showed statistically insignificant variance in daily dosage among insulin detemir and insulin glargine in T2D cases.
Raskin et al. (11) aimed to assess the safety and efficacy of insulin detemir and insulin glargine within a basal-bolus protocol with insulin aspart in type 2 diabetes. They observed statistically insignificant distinction among insulin detemir and GLA concerning daily dosage.

Conclusion

Our research revealed that no difference has been observed in the continuation of any non-insulin anti-diabetic medicines among cases receiving insulin detemir and those receiving insulin glargine. The most prevalent concurrent non-insulin glucose-lowering drug was metformin. The average daily insulin usage is comparable among insulin detemir and insulin glargine; hence, neither must be favored over the other.

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