Review Article :

Evaluation of Insulin and Glucagon-like peptide-1 Receptor Agonists Combination for Type 2 Diabetes Mellitus: An Updated Meta-analysis.

Raed Aldahash[1,2,3], Khaled K. Al Dossari [4], Faisal Holil AlAnazi [5], Ahmed Salah Hussein[6]

1. Department of Medicine, Ministry of National Guard Health Affairs, Saudi Arabia
2.King Abdullah International Medical Research Center, Saudi Arabia
3.King Saud Bin Abdulaziz for Health Science University, Riyadh, Saudi Arabia
4.Department of Family and Community Medicine, College of Medicine, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942
5.Department of Medicine, College of Medicine, Majmaah University, Majmaah, Saudi Arabia
6.Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Received on Apr 03, 2023, accepted for publication on May 10, 2024, dx.doi.org/10.5455/mjhs.2024.03.015

Corresponding author:

Dr. Ahmed Salah Hussein
Shibin Al-Qanatir, Qalyubia, Egypt
Faculty of Medicine, Al-Azhar University, Cairo, Egypt
+20/1158276261 - Email: ahmedsalah2230@azhar.edu.eg

OPEN ACCESS Distributed under Creative Commons CC BY-NC-ND 4.0

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RA) increase glucose-stimulated insulin secretion, suppress glucagon production, increase satiety, reduce food intake, improve insulin sensitivity, and reduce visceral fat. This study aims to compare the GLP-1RA and insulin combination or GLP-1RA added to background insulin therapy with other injectable therapies in patients with type-2 diabetes mellitus (T2DM). We searched for studies that compared GLP-1RA and insulin combination with other injectable therapies in T2DM patients for HbA1c (%) change, achieving HbA1c <7% at study end, hypoglycemia incidence, and weight change. The following intervention groups were analyzed: the combination of basal insulin and GLP-1RA, basal-plus/basal-bolus, and placebo/insulin intensification (insulin up-titration)/GLP-1RA. A total of 48 studies were included. Insulin and GLP-1RA combination therapy reduced HbA1c more than placebo/insulin intensification (insulin up-titration)/GLP-1RA (WMD -0.693, p <0.001) and basal-plus/basal-bolus (WMD -0.105, p =0.027). Insulin and GLP-1RA combination therapy significantly reduced body weight more than placebo/insulin intensification (insulin up-titration)/GLP-1RA (WMD -1.894, p <0.001) and basal-plus/basal-bolus (WMD -3.6, p =0.001). Patients on insulin and GLP-1RA combination therapy had a higher chance of achieving the HbA1c target than placebo/insulin intensification (insulin up-titration)/GLP-1RA arm (RR 1.964, p <0.001), but not than basal-plus/basal-bolus arm (RR 1.037, 95% CI 0.971 to 1.103). Hypoglycemia rates were comparable between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA (RR 0.94, 95% 0.84 - 1.04), but statistically significant when compared to combination therapy and basal-plus/basal-bolus (RR 0.63, p <0.001). Our findings support using GLP-1RA in combination with insulin as a useful intensification approach for producing therapeutic improvement in T2DM therapy for individuals who have not reached their HbA1c goal.

Keywords:
basal insulin, glucagon-like peptide-1 receptor agonists, type 2 diabetes mellitus, glycaemic control, meta-analysis.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disorder that causes long-term vascular consequences and death globally. Per the International Diabetes Federation's most recent estimates, 463 million individuals had diabetes in 2019, with the figure expected to climb to 700 million by 2045. [1–3]

Because of the natural history of diabetes and the steady loss in β-cell activity, insulin often becomes necessary. Nevertheless, insulin therapy is hampered by challenging factors such as hypoglycemia risk, weight gain, and the complexities of injectable therapy. [4] Approximately 25% of T2DM patients are now on insulin. [5,6] However, about one-half of T2DM patients who take insulin achieve optimal control of diabetes, and the number of individuals with HbA1c of 9% or more is rapidly rising. [5,7] A recent consensus report documented that intensification approaches should be customized based on the patient factors (such as glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels). [8]

Glucagon-like peptide-1 receptor agonists (GLP-1RA) boost glucose-stimulated insulin secretion, inhibit glucagon production, enhance satiety, reduce food intake, improve insulin sensitivity, and reduce deposition of visceral fat. 9 GLP1RA lowers HbA1c by up to 1.8% and has a minimal hypoglycemia risk while also lowering weight, blood pressure, and lipid profile. [10]

Basal insulins combined with GLP-1RA are an efficient therapeutic choice for T2DM patients who require insulin therapy intensification. Insulin degludec (IDeg) combined with liraglutide [IDegLira], as well as insulin glargine (IGlar) combined with lixisenatide [iGlarLixi], are two combination medications (fixed-ratio combo) with set dosages of long-acting insulins and GLP-1RA, which are now authorized.[8]

In the DUAL studies, IDegLira improved glycemic control alongside bodyweight benefits and equivalent or reduced rates of hypoglycemic episodes compared to basal insulin, as well as a decreased risk of gastrointestinal side effects compared to GLP-1RAs alone.[11–15] Previous literature has mentioned that iGlarLixi might offer reasonable glycemic control rather than administering the two medications separately. The fixed-ratio combination's better

efficacy is due to the complementary nature of the combined medications, the ease of administration and titration, and the decrease in adverse effects. [16,17]

We conducted the current meta-analysis of randomized controlled trials (RCTs) published until December 2021 that compared combination therapy with other injectable therapies in T2DM patients.

Methods

This systematic review and meta-analysis has been conducted in accordance with the guidelines outlined in the "preferred reporting items for systematic review and meta-analysis (PRISMA) statement". [18]

Literature search strategy

We searched PubMed, Scopus, EBSCO, and Web of Science using a search strategy including the following search terms: "biphasic insulin regimen," "premixed insulin," "basal plus insulin regimen," "basal-bolus insulin regimen," "glargine," "degludec," "detemir," "aspart," "glulisine," "lispro," "glucagon-like peptide-1 receptor agonist", "GLP-1 receptor agonist", "GLP-1RA", "exenatide," "exenatide LAR," " liraglutide," " lixisenatide," " dulaglutide," " semaglutide," " albiglutide," " IDegLira," and" IGlarLixi" through December 2021.

Study eligibility

Inclusion criteria

We included the RCTs satisfying the following criteria:

Population: adults with type 2 diabetes mellitus

Intervention and comparison: a combination of GLP-1RA and insulin (whether fixed ratio or free combination) or GLP-1RA added to background insulin therapy compared with other injectable therapies, including placebo/insulin intensification (insulin up-titration)/GLP-1RA; or basal-plus/basal-bolus therapies.

Outcomes: HbA1c (%) change, the proportion of patients achieving HbA1c <7% at the study end, the incidence of blood glucose-confirmed symptomatic hypoglycemia, and weight change

Exclusion criteria

We excluded non-RCTs, reviews with no original data, studies with insufficient data, case reports, case series, letters to the editor, as well as studies on patients other than T2DM.

Study selection

Initially, the titles and abstracts of the retrieved records were assessed to determine whether they met the eligibility criteria, after which the full text of potentially relevant records was examined to further assess their eligibility. We searched for

RCTs that looked at GLP-1RA and insulin combination compared with other injectable therapies in adults with T2DM in terms of the HbA1c (%) change, the proportion of patients achieving HbA1c <7% at the study end, the incidence of blood glucose-confirmed symptomatic hypoglycemia, and weight change.

Data extraction

We extracted the following data for all of the included studies

1- Demographic data

Study ID with the year of publication, design of the study, duration of the study (weeks), studied arms, the total number of the included patients in each group, mean age (years), as well as baseline levels of HbA1c, and the primary outcome.

2- Study outcomes

For each study arm, we retrieved data about HbA1c, and weight change as well as the incidence of hypoglycemias (safety).

Risk of bias assessment

To assess the quality of the RCTs included in the study, the Cochrane risk of bias assessment tool was utilized. This tool evaluates various aspects of the RCTs, including sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other factors that could potentially introduce bias into the study. There are three levels of potential bias assigned to the decision: low, high, and unclear.

Statistical analysis

Data analysis was performed using SPSS version 28.0 software for Windows. The effect size of continuous data was obtained according to Tierney et al. [19] and was pooled using weighted mean difference (WMD). Dichotomous data were pooled as a risk ratio (RR) using a random-effects model. According to Cochrane Handbook recommendations, heterogeneity was inspected visually and statistically through Chi-square and I^2 tests, and P<0.1 was designated as a level of significant heterogeneity. Upon detecting significant heterogeneity, we employed further sensitivity analyses to determine the source of heterogeneity by excluding one study at a time. Furthermore, we employed a comparison-adjusted funnel plot for each outcome, which displayed asymmetries for all interventions with a significant Egger's test revealing a small-study effect. The funnel plot is a scatter diagram showing the distribution of studies, precision, and outcome measures. A single direct comparison is shown by each dot. Idealized dispersion owing to sample variance should resemble a pyramid or an inverted funnel on the

plot. An asymmetrical funnel plot means publication/reporting bias, poor methodological design, or heterogeneity.

Results

The search strategy retrieved 3100 unique records; of them, 2995 records were excluded after title/abstract screening, while the remaining 105 records were sought for retrieval. Thus, 48 studies [11,12,14–17,20–61] were included in the present study, Supplementary Figure 1. The summary characteristics of the included studies are shown in Table 1 (a and b). Supplementary Table 1 displays the outcomes of the assessment of the risk of bias.

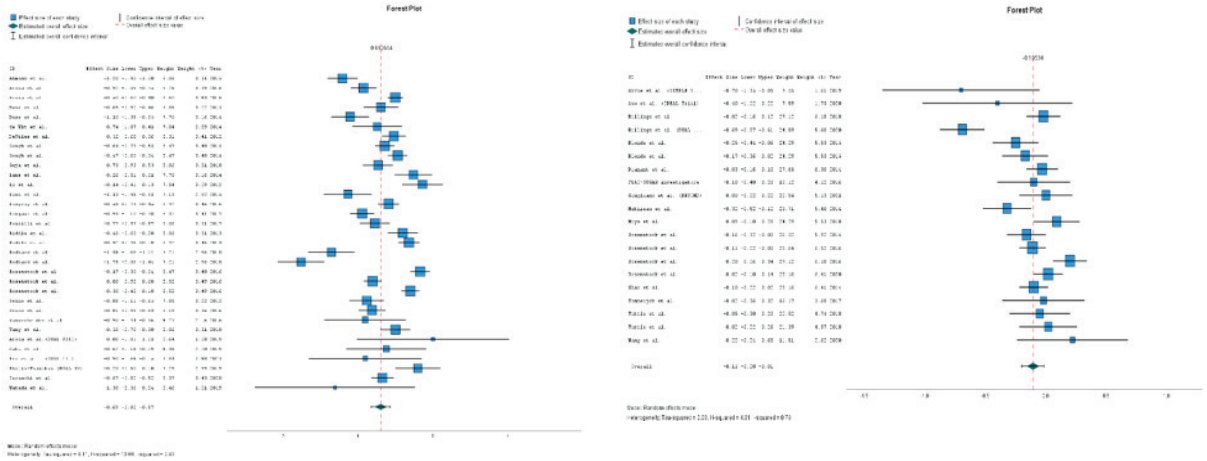


Figure 1: (a) forest plot of the pooled estimate for the comparison of the change in HbA1c level (%) between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA, (b) forest plot of the pooled estimate for the comparison of the change in HbA1c level (%) between combination therapy and basal-plus/basal-bolus.

Table 1 (a) presents the summary characteristics of the included double-blind randomized clinical trials.

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Pei et al. 2021 (DUAL II China) [21]a randomized, double-blinded, multicentre, treat-to-target trial, Chinese adults with T2D and HbA1c of 7.5% or more on basal insulin and metformin, with or without other oral antidiabetic drugs (OADs	26	IDegLira	302	54.5 (9.8)	8.93 (1.20)	HbA1c change from baseline after 26 weeks of treatment
		Degludec	151	55.3 (10.0)	8.96 (1.17)	
Watada et al. 2019 [25]	26	Insulin degludec/liraglutide (IDegLira)	105	56.6 (10.4)	8.61 (0.88)	Change from baseline in HbA1c after 26 weeks of treatment
		Insulin degludec (degludec)	105	55.5 (10.0)	8.56 (0.80)	
Buse et al, 2011 [26]randomized, placebo-controlled trial, blocked and stratified by HbA1c level at site, performed from October 2008 to January 2010. Participants, investigators, and personnel conducting the study were masked to treatment assignments. (ClinicalTrials.gov registration number: NCT00765817	30	Exenatide 10 µg BID	138	59 (9)	8.3 (0.8)	HbA1c levels at week 30
		Placebo	123	59 (10)	8.5 (0.9)	

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Seino et al, 2012 (Get-Goal-L-Asia) [29]randomized, double-blind, placebo-controlled, parallel-group, multicentre study, participants (mean baseline HbA1c 8.53%	24	Lixisenatide 20 µg	154	58.7 (10.2)	8.5 (0.7)	Change in HbA1c to week 24
		Placebo	157	58.0 (10.1)	8.5 (0.8)	
Riddle et al, 2013 (Get-Goal-L) [30]in people with type 2 diabetes and elevated glycated hemoglobin (HbA1c	24	Lixisenatide 20 µg	328	57 (10)	8.4 (0.9)	Change in HbA1c to week 24
		Placebo	167	57 (10)	8.4 (0.8)	
Riddle et al, 2013 (GetGoal-Duo 1) [31]adding basal insulin improves glycemic control. However, when glycated hemoglobin (HbA1c	24	Lixisenatide 20 µg	223	56 (10)	7.6 (0.5)	Change in HbA1c to week 24
		Placebo	223	56 (10)	7.6 (0.5)	
Buse et al, 2014 (DUAL II) [12]double-blind trial, patients with type 2 diabetes (A1C 7.5 -10.0% [58- 86 mmol/mol]	26	IDegLira + Metformin	207	57 (9)	8.7 (0.7)	Change in HbA1c to week 26
		Degludec + Metformin titration	206	58 (11)	8.8 (0.7)	
Ahmann et al, 2015 (LIRA-ADD2BASAL) [34]compared with placebo, of adding liraglutide to pre-existing basal insulin analogue±metformin in adults with inadequately controlled type 2 diabetes [glycated haemoglobin (HbA1c	26	Liraglutide 1.8 mg	226	59.3 (9.2)	8.2 (0.8)	Change in HbA1c to week 26
		Placebo	225	57.5 (11.1)	8.3 (0.9)	
Lind et al, 2015 (MDI Liraglutide trial) [35]an incretin based treatment, on glycaemic control in people with type 2 diabetes treated with multiple daily insulin injections? Methods The study was a randomised, double blind, placebo controlled trial with a parallel group design carried out at 13 hospital based outpatient clinics and one primary care unit in Sweden. Patients were considered eligible for inclusion if they had type 2 diabetes and inadequate glycaemic control (HbA1c concentrations ≥58 mmol/mol (7.5%	24	Liraglutide 1.8 mg	64	63.8 (8.2)	9.0 (1.0)	Change in HbA1c to week 24
		Placebo	60	63.5 (7.7)	9.0 (1.1)	
Aroda et al, 2016 (BEGIN:ADD TO GLP-1 Study) [36]double-blind trial, patients who still had inadequate glycaemic control after a 15-week run-in period with initiation and dose escalation of liraglutide to 1.8 mg in combination with metformin (≥1500 mg	26	Degludec	174	57 (10)	7.6 (0.6)	Change in HbA1c to week 26
		Placebo	172	57.3 (9.4)	7.6 (0.6)	
Seino et al, 2016 [38]	36	Liraglutide 0.9 mg	127	61.3 (11)	8.8 (0.9)	Change in HbA1c to week 16
		Placebo	130	59.8 (11.3)	8.8 (0.9)	
Vanderheiden et al, 2016 [39]hypoglycemia, and high treatment burden. OBJECTIVE To assess the effectiveness and safety of adding a glucagon-like peptide 1 receptor agonist to the treatment regimen of patients with type 2 diabetes requiring therapy with high-dose insulin. DESIGN, SETTING, AND PARTICIPANTS This clinical trialwas a double-blind, placebo-controlled, randomized (1:1	24	Liraglutide 1.8 mg	35	52.8 (8.1)	9.0 (1.2)	Change in HbA1c to week 24
		Placebo	36	55.5 (6.6)	8.9 (1.0)	
Pozzilli et al, 2017 (AWARD-9) [41]	28	Dulaglutide 1.5 mg	150	60.2 (9.5)	8.4 (0.9)	Change in HbA1c to week 28
		Placebo	150	60.6 (10.1)	8.3 (0.8)	
Guja et al, 2018 (DURATION-7) [42]double-blind study (ClinicalTrials.gov identifier: NCT02229383	28	Exenatide LAR 2 mg	231	57.8 (9)	8.5 (0.9)	Change in HbA1c to week 28
		Placebo	230	57.6 (10.3)	8.5 (0.9)	

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Rodbard et al, 2018 (SUSTAIN-5) [43]	30	Semaglutide 0.5 mg	132	59.1	8.4	Change in HbA1c to week 30
		Semaglutide 1 mg	131	58.5	8.3	
		Placebo	133	58.8	8.4	
Yang et al, 2018 (GetGoal-L-C) [44]during which BI was titrated to a target self-monitored plasma glucose (SMPG; 4.4-5.6 mmol/L	24	Lixisenatide 20 µg	224	53.9 (9.9)	7.9 (0.6)	Change in HbA1c to week 24
		Placebo	224	56.2 (9.1)	7.9 (0.7)	

Table 1 (b) presents the summary characteristics of the included open-label trials.

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Abrue et al. 2019 (SIMPLE Study) [57]	24	Basal Insulin + GLP1RA Group	59	46.7 (9.0)	12.1 (1.4)	Change in HbA1c; changes in weight, insulin dose, hypoglycemia
		Basal-Bolus Insulin Group	61	48.1 (10.0)	12.0 (1.5)	
Aroda et al. 2019 (DUAL VIII) [58]multicentre, open-label, phase 3b randomised controlled trial, insulin-naive patients aged 18 years and older, with HbA1c between 7·0–11·0% (53–97 mmol/mol	104	Insulin degludec plus liraglutide (IDegLira)	506	56.8 (10.0)	8.4% (1.0)	Time from randomization to need for treatment intensification
		Insulin glargine 100 units/Ml (IGlar U100)	506	56.4 (10.1)	8.6% (1.0)	
Aso et al. 2020 [59]HbA1c decreased by 0.3% in the IDegAsp group and by 0.7% in the IDeg + Lira group. The HbA1c reduction was greater in the IDeg + Lira group than in the IDegAsp group. 19% of patients on IDegAsp versus 40% on IDeg + Lira achieved HbA1c < 7.0%. Pre-breakfast and pre-dinner blood glucose at 52 weeks were significantly lower in the IDeg + Lira group than in the IDegAsp group. The reduction in body mass index (BMI	52	Insulin degludec/ insulin aspart (IDegAsp)	28	68.8 (8.9)	8.2 (0.9)	HbA1c changes over 52 weeks of treatment, and the percentage of participants achieving HbA1c<7.0% at week 5 2
		Basal insulin degludec and liraglutide (IDeg+Lira)	24	6 8.0 (10.4)	7.9 (0.6)	
Billings et al. 2020 (DUAL VII) [60]	26	Insulin Degludec/Liraglutide (IDegLira)	238	<65= 170 of 238 & ≥65= 68 of 238		Change in HbA1c from baseline to week 26
		Basal-Bolus Insulin Group	233	<65= 184 of 233 & ≥65= 48 of 233		
Giugliano et al. 2021 (BEYOND) [61]2	24	Intensification of the basal-bolus insulin (BBI) regimen	101	62.1 ± 10.2	8.5 (1.1)	Change from baseline in HbA1c at 6 months
		A fixed ratio of basal insulin plus GLP-1RA (fixed-combo group)	102	62.6 ± 9.6	8.5 (1.0)	
Kaku et al. 2019 [20]	52	Insulin degludec/liraglutide (IDegLira)	275	56.9 (10.2)	8.5 (1.1)	Change from baseline in HbA1c after 52 weeks of treatment
		Degludec	271	57.8 (9.9)	8.5 (1.1)	
		Liraglutide 1.8	273	56.8 (10.1)	8.3 (1.0)	

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Philis-Tsimikas 2019 (DUAL IX) [15]	26	Insulin Degludec/Liraglutide (IDegLira)	210	56.1 (10.4)	8.2 (0.9)	Change in HbA1c from baseline to week 26
		Insulin Glargine U100	210	57.2 (10.2)	8.4 (1.1)	
Rosenstock et al. 2020 [22]basal plus prandial insulin was optimized over 4 weeks before participants were randomized (1:1	26	Albiglutide + glargine	402	58.0 (9.4)	7.7 (0.6)	Change from baseline in HbA1c at 26 weeks
		Lispro + glargine	412	58.1 (9.5)	7.7 (0.6)	
Terauchi et al. 2020 [23]multicentre, open-label, 1:1 randomized, parallel-group study compared efficacy of iGlarLixi and iGlar in patients with T2DM, HbA1c of ≥7.5% to ≤9.5% and fasting plasma glucose ≤10.0 mmol/L (180 mg/dL	26	Insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi)	260	59.2 (11.0)	8.08 (0.50)	Change in HbA1c from baseline to week 26.
		Insulin glargine U100 (iGlar)	261	60.2 (10.3)	8.01 (0.45)	
Wang et al. 2020 [24]defined as 24-h urinary albumin excretion rate (UAER	24	Exenatide twice daily plus insulin glargine (intervention group)	46	55.9 (8.9)	9.1 (1.4)	Urinary albumin excretion rate percentage change from the baseline after 24 weeks of intervention
		Insulin lispro plus glargine (control group)	46	55.9 (8.9)	9.0 (1.3)	
DeVries et al, 2012 [27]sulfonylurea was discontinued and liraglutide 1.8 mg/day added for 12 weeks (run-in	26	Detemir	162	56.8 (9.4)	7.6 (0.6)	Change in HbA1c to week 26
		Continuing metformin + liraglutide 1.8 mg	161	57.3 (9.8)	7.6 (0.7)	
Li et al, 2012 [28]randomized, parallel-group study was carried out. A total of 84 patients completed the trial who had been randomly assigned to either the liraglutide-added group or the insulin-increasing group while continuing current insulin based treatment. Insulin dose was reduced by 0-30% upon the initiation of liraglutide. Insulin doses were subsequently adjusted to optimized glycemic control. Glycosylated hemoglobin (HbA1c	12	Liraglutide 1.2 mg	42	51.2 (10.5)	8.8 (0.8)	HbA1c levels at week 12
		Insulin up-titration	42	52.7 (10.8)	8.7 (0.9)	
de Wit et al, 2014 (ELEGANT) [32]	26	Liraglutide 1.8 mg	26	57 (10)	7.2 (0.6)	Change in body weight to week 26
		Intensification of insulin therapy	24	59 (8)	7.5 (0.7)	
Gough et, al 2014 (DUAL-I) [11]	26	IDegLira	834	55.1 (9.9)	8.3 (0.9)	Change in HbA1c to week 26
		Degludec Titration	414	54.9 (9.7)	8.3 (1.0)	
		Liraglutide 1.8 mg	415	55.0 (10.2)	8.3 (0.9)	
Lane et al, 2014 [33]2]. The effect of GLP-1 RA therapy added to intensive (basal/bolus	24	Liraglutide 1.8 mg	21	59 (11.8)	7.8 (0.6)	HbA1c at week 24
		Insulin up-titration	16	60.8 (9.7)	7.8 (0.7)	
Aroda et al, 2016 (LixiLan-L) [16]a novel, titratable, fixed-ratio combination of insulin glargine (iGlar	30	IGlarLixi	367	59.6 (9.4)	8.1 (0.7)	Change in HbA1c to week 30
		Glargine titration	369	60.3 (8.7)	8.1 (0.7)	
Lingvay et al, 2016 (DUAL V) [14]	26	IDegLira	278	58.4 (9.8)	8.4 (0.9)	Change in HbA1c to week 26
		Glargine titration	279	59.1 (9.3)	8.2 (0.9)	

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Rosenstock et al, 2016 (Lixilan PoC) [37]a fixed-ratio, titratable, combination of 2 units insulin glargine (Gla-100	24	IGlarLixi	161	56.9 (9.5)	8.1 (0.8)	Change in HbA1c to week 24
		Glargine titration	162	56.6 (9.4)	8.0 (0.8)	
Rosenstock et al, 2016 (LixiLan-O) [17]a novel titratable fixed-ratio combination of insulin glargine (iGlar	30	IGlarLixi	469	58.2 (9.5)	8.1 (0.7)	Change in HbA1c to week 30
		Glargine titration	467	58.3 (9.4)	8.1 (0.7)	
		Lixisenatide 20 µg	234	58.7 (8.7)	8.1 (0.7)	
Linjawi et al, 2017 (DUAL III) [40]followed by other agents, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs	26	IDegLira	292	58.3 (9.9)	7.8 (0.6)	Change in HbA1c to week 26
		Liraglutide or Exenatide at their pre-trial dose	146	58.4 (8.8)	7.7 (0.6)	
Diamant et al, 2014 (4B Study) [45]this complex regimen is associated with weight gain and hypoglycemia. This study compared the efficacy and safety of exenatide twice daily or mealtime insulin lispro in patients inadequately controlled by insulin glargine and metformin despite up-titration.\nRESEARCH DESIGN AND METHODS In this 30-week, open-label, multicenter, randomized, noninferiority trial with 12 weeks prior insulin optimization, 627 patients with insufficient postoptimization glycated hemoglobin A1c (HbA1c	30	Exenatide 10 µg BID	315	59.8 (9.5)	8.3 (1.0)	Change in HbA1c to week 30
		Lispro thrice daily	312	57.4 (8.9)	8.2 (0.9)	
Mathieau et al, 2014 (BEGIN: VICTOZA ADD-ON) [46]mean HbA1c: 7.7% (61mmol/mol	26	Liraglutide 1.8 mg	88	61.1 (9.5)	7.7 (0.6)	Change in HbA1c to week 26
		Aspart at largest meal	89	60.9 (8.8)	7.7 (0.8)	
Rosenstock et al, 2014 (Harmony 6) [47]open-label, activecontrolled trial testing once-weekly albiglutide vs. thrice-daily prandial insulin lispro as an add-on to titrated once-daily insulin glargine. RESEARCH DESIGN AND METHODS: Patients taking basal insulin(with or without oral agents	26	Albiglutide 30 mg	282	54.8 (9.1)	8.5 (0.9)	Change in HbA1c to week 26
		Lispro thrice daily	281	56.3 (8.9)	8.4 (0.9)	
Shao et al, 2014 [48]	12	Exenatide 10 µg BID	30	43 (4.1)	7.6 (0.6)	HbA1c at week 12
		Aspart thrice daily	30	42 (3.2)	7.7 (0.6)	

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Blonde et al, 2015 (AWARD-4) [49]advancing to a basal-bolus insulin regimen is often recommended. We aimed to compare the efficacy and safety of long-acting glucagon-like peptide-1 receptor agonist dulaglutide with that of insulin glargine, both combined with prandial insulin lispro, in patients with type 2 diabetes. Methods We did this 52 week, randomised, open-label, phase 3, non-inferiority trial at 105 study sites in 15 countries. Patients (aged ≥18 years	52	Dulaglutide 1.5 mg	295	58.9 (9.6)	8.5 (1.1)	Change in HbA1c to week 26
		Dulaglutide 0.75 mg	293	59.3 (9.0)	8.4 (1.0)	
		Glargine titration	296	59.9 (9.1)	8.5 (1.0)	
FLAT-SUGAR investigators, 2016 [50]which may worsen outcomes by inducing inflammation, oxidative stress, and cardiac arrhythmias. We tested whether a glucagon-like peptide 1 agonist-based regimen can reduce GV and cardiometabolic risk markers while maintaining similar A1C levels in people with insulin-requiring type 2 diabetes and high cardiovascular risk. RESEARCH DESIGN AND METHODS After run-in on metformin and basal-bolus insulin (BBI	26	Exenatide 5-10 µg	52	62	7.9 (0.3)	Change in glucose coefficients of variation to week 26
		Short-acting insulin analogs thrice daily	50	62	7.9 (0.3)	
Rosenstock et al, 2016 (GetGoal Duo-2) [51]we explored head-to-head prandial interventions in overweight patients with type 2 diabetes inadequately controlled on basal insulin glargine with or without 1-3 oral antidiabetic agents (OADs	26	Lixisenatide 20 µg	298	59.8 (8.6)	7.8 (0.6)	Change in HbA1c to week 26
		Glulisine once daily	298	60.2 (8.6)	7.7 (0.6)	
		Glulisine thrice daily	298	59.4 (9.5)	7.8 (0.6)	
Tonneijck et al, 2017 [52]a prandial short-acting glucagon-like peptide receptor agonist (GLP-1RA	8	Lixisenatide 20 µg	17	62 (7)	8.3 (0.2)	Change in Glomerular filtration rate and effective renal plasma flow to week 8
		Glulisine once daily	18	61 (7)	7.8 (0.2)	
Billings et al, 2018 (DUAL VII) [53]	32	IDegLira	25,2	58.6 (9.0)	8.2 (0.8)	Change in HbA1c to week 26
		Glargine and Insulin Aspart four or fewer times daily	254	58.0 (8.6)	8.2 (0.8)	
Miya et al, 2018 [54]	12	Lixisenatide 20 µg plus insulin glargine	11	66 (8.4)	7.1 (0.5)	Change in the Diabetes Treatment Satisfaction Questionnaire scores to week 12
		Continuing Multiple daily injections of insulin	15	59.6 (12.8)	7.2 (0.9)	

Author, year (trial name)	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Primary outcome
Tuttle et al, 2018 (AWARD-7) [55]including insulin, are primarily cleared by the kidneys, restricting treatment options for patients with kidney disease. Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist that is not cleared by the kidneys, and confers a lower risk of hypoglycaemia than does insulin. We assessed the efficacy and safety of dulaglutide in patients with type 2 diabetes and moderate-to-severe chronic kidney disease. Methods: AWARD-7 was a multicentre, open-label trial done at 99 sites in nine countries. Eligible patients were adults with type 2 diabetes and moderate-to-severe chronic kidney disease (stages 3–4	52	Dulaglutide 1.5 mg	192	64.7 (8.8)	8.6 (0.9)	HbA1c at 26 weeks
		Dulaglutide 0.75 mg	190	64.7 (8.6)	8.6 (1.1)	
		Glargine titration	194	64.3 (8.4)	8.6 (1.0)	
Yamamoto et al, 2018 [56]	24	Liraglutide 0.9 mg and basal insulin	13	60.0 (7.8)	7.3 (1.2)	Change in HbA1c to week 24
		Continuing basal bolus insulin therapy	12	61.5 (10.6)	6.9 (0.8)	

Meta-analysis characteristics

Different intervention groups were analyzed as follows: the combination between basal insulin and GLP-1RA (fixed-ratio or free combination), basal-plus/basal-bolus, and placebo/insulin intensification (insulin up-titration)/GLP-1RA.

The Change in HbA1c (%)

Thirty-three studies reported reliable data for the comparison of the change in HbA1c level between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA. The mean change from baseline in the HbA1c was significantly higher in the combination arm than in the control arm (WMD -0.693, 95% CI -0.818 to -0.567; p <0.001). The pooled analysis was substantially heterogeneous (I2 =93%; Figure 1A). Heterogeneity was not resolved after further sensitivity analysis. The trim-and-fill analysis of publication bias imputed 33 missing studies for this comparison, donating significant publication bias (p <0.001), confirmed by an asymmetrical funnel plot (Supp. Figure 2A).

On the other hand, 20 studies compared the change in HbA1c level between combination therapy and basal-plus/basal-bolus. Again, the pooled analysis favoured the combination regimen (WMD -0.105, 95% CI -0.199 to -0.012; p =0.027), with substantial heterogeneity (I2 =79%; Figure 1B) that could not be resolved by further sensitivity analysis. The trim-and-fill analysis of publication bias imputed 20 missing studies for this comparison, donating sig-

nificant publication bias, confirmed by an asymmetrical funnel plot (Supp. Figure 2B).

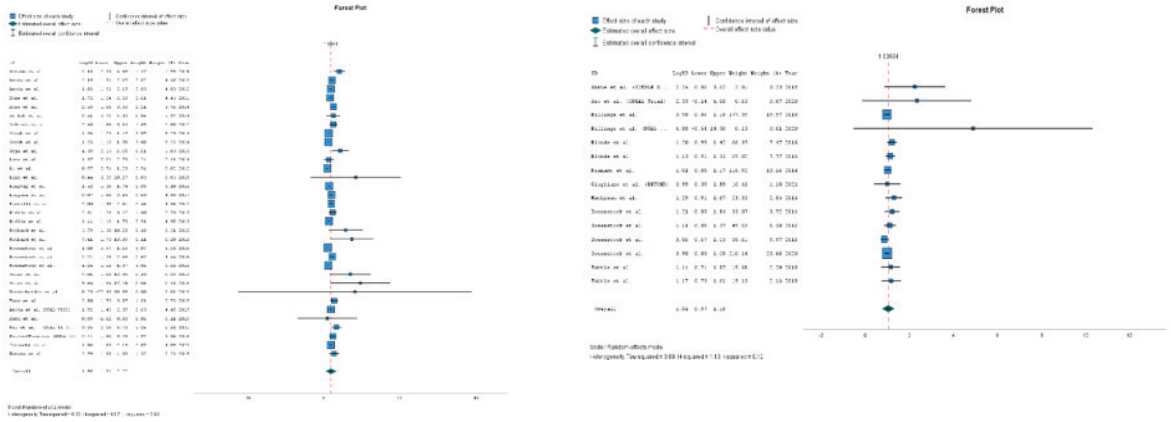


Figure 2: (a) forest plot of the proportion of patients achieving the targeted HbA1c between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA, (b) forest plot of the proportion of patients achieving the targeted HbA1c between combination therapy and basal-plus/basal-bolus.

The proportion of patients achieving the targeted HbA1c (%)

The pooled analysis of the 33 studies reported comparing the proportion of patients achieving the targeted HbA1c between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA showed that patients on combination therapy had a higher chance of achieving the HbA1c target (RR 1.964, 95% CI 1.708 to 2.22; p <0.001). The pooled analysis was substantially heterogeneous (I2 =93%; Figure 2A). Heterogeneity was not resolved after further sensitivity analysis. The trim-and-fill analysis of publication bias imputed 43 missing studies for this comparison donating significant publication bias (p <0.001), confirmed by an asymmetrical funnel plot (Supp. Figure 3A)

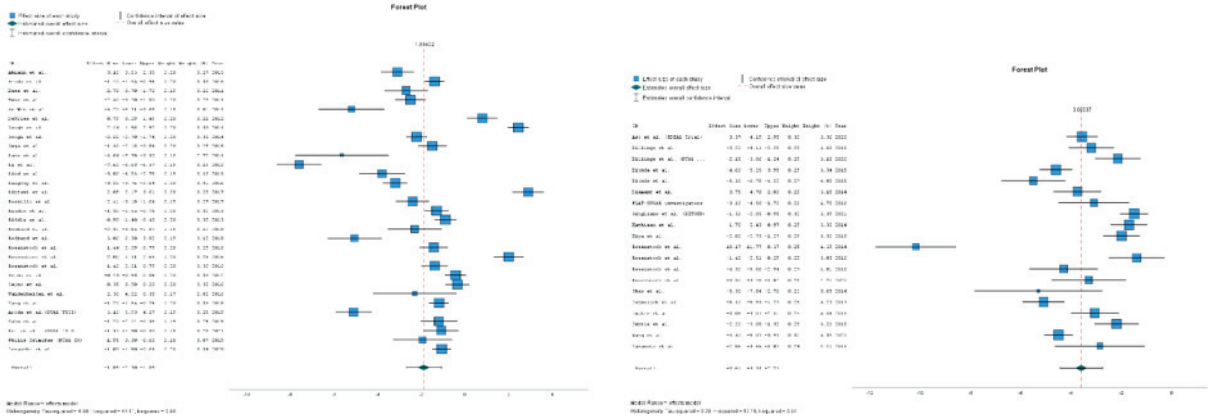


Figure 3: (a) forest plot of the pooled estimate for the change in body weight between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA, (b) forest plot of the pooled estimate for the change in body weight between combination therapy and basal-plus/basal-bolus.

On the contrary, the 15 studies comparing combination therapy and basal-plus/basal-bolus showed no significant difference (RR 1.037, 95% CI 0.971 to 1.103), with no significant heterogeneity (I2 =12%; Figure 2B) that could not be resolved by further sensitivity analysis. The trim-and-fill analysis of publication bias imputed 21 missing studies for this comparison, donating significant publication bias, confirmed by an asymmetrical funnel plot (Supp. Figure 3B).

The change in body weight (Kg)

Thirty-one compared the change in body weight between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA. The mean reduction from baseline in body weight was significantly higher in the combination arm than in the control arm (WMD -1.894, 95% CI -2.697 to -1.091; p <0.001). The pooled analysis was substantially heterogeneous (I2 =98%; Figure 3A). Heterogeneity was not resolved after further sensitivity analysis. The trim-and-fill analysis of publication bias imputed 31 missing studies for this comparison, donating significant publication bias (p <0.001), confirmed by an asymmetrical funnel plot (Supp. Figure 4A).

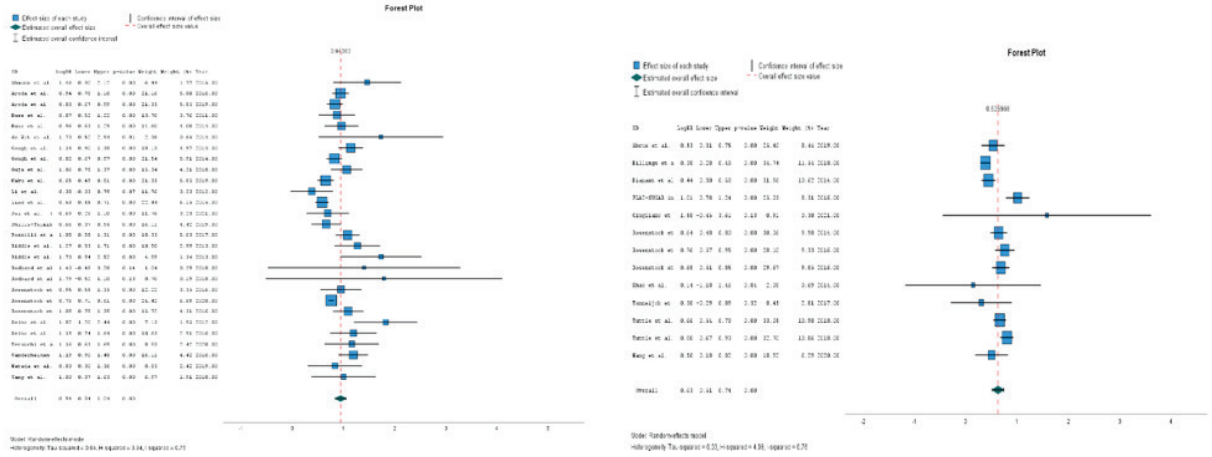


Figure 4: (a) forest plot of the pooled estimate for the incidence of hypoglycaemia between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA, (b) forest plot of the pooled estimate for the incidence of hypoglycaemia between combination therapy and basal-plus/basal-bolus.

On the other hand, 20 studies compared the change in body weight between combination therapy and basal-plus/basal-bolus. Again, the pooled analysis favoured the combination regimen (WMD -3.6, 95% CI -4.435 to -2.766; p =0.001), with substantial heterogeneity (I2 =94%; Figure 3B) that could not be resolved by further sensitivity analysis. The trim-and-fill analysis of publication bias imputed 20 missing studies for this comparison, donating significant publication bias, confirmed by an asym-

metrical funnel plot (Supp. Figure 4B).

The incidence of hypoglycemia

The pooled analysis of the 32 studies comparing the proportion of patients with confirmed hypoglycemia between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA showed comparable rates (RR 0.94, 95% 0.84 - 1.04). The pooled analysis was substantially heterogeneous (I2 =75%; Figure 4A). Heterogeneity was not resolved after further sensitivity analysis. The trim-and-fill analysis of publication bias imputed eight missing studies for this comparison, donating significant publication bias (p <0.001), confirmed by an asymmetrical funnel plot (Supp. Figure 5A).

On the contrary, the 13 studies comparing combination therapy and basal-plus/basal-bolus showed a statistically significant difference (RR 0.63, 95% CI 0.51 - 0.74; p <0.001), with no significant heterogeneity (I2 =76%; Figure 4B) that could not be resolved by further sensitivity analysis. The trim-and-fill analysis of publication bias no imputed missing studies for this comparison donating no significant publication bias, confirmed by a symmetrical funnel plot (Supp. Figure 5B).

Discussion

Given the progressive nature of T2DM, many patients require insulin to attain their desired glycemia. Since 2019, when injectable therapy is necessary, the American Diabetes Association has advised GLP-1RA before basal insulin. [62] A basal insulin single injection is a standard way to begin insulin therapy, gradually increasing to maximize therapy. Adding premeal rapid-acting insulin analogues to the continuing dose of basal insulin or switching to a premixed insulin regimen with a predetermined dosage of "intermediate-acting: and "short- or rapid-acting" insulin are two ways to increase insulin therapy to reach glycaemic goals. Even though these regimens of intensified insulin results in the same drop in HbA1c, [63,64] people are often reluctant to intensify insulin therapy because of possible side effects like the risk of hypoglycemia and gaining weight, as well as practical issues such as patients' anxiety regarding insulin and difficulties in teaching patients of injections. Thus, combining GLP-1RA with insulin may give a unique and effective treatment alternative for improving glycemic control while reducing the risks of insulin intensification.

Summary of main findings

The current updated systematic review and meta-analysis of RCTs aimed to compare the combination therapy with other injectable therapies in T2DM patients. Compared to placebo/insulin intensification

(insulin up-titration)/GLP-1RA alone, the combination resulted in a higher decline in HbA1c levels, with more patients reaching the HbA1c target of 7%, weight loss, and a comparable risk of hypoglycemia. Moreover, the combination led to a higher decline in HbA1c, weight loss, lower risk of hypoglycemia, and a comparable proportion of patients reaching the HbA1c target of 7%. A previous meta-analysis published in 2019 showed that compared to placebo, insulin up-titration, or GLP-RA alone, the combination resulted in a larger HbA1c reduction, with more patients reaching the HbA1c goal of 7%, a higher risk of hypoglycemia, and weight loss, and was as effective as insulin regimens, with less hypoglycemia and weight loss. [65]

In the currently updated meta-analysis, in terms of change in HbA1c (%), the combination therapy of insulin and GLP-1RA significantly reduced HbA1c (%) than the placebo/insulin intensification (insulin up-titration)/GLP-1RA arm (WMD -0.693, p <0.001) and basal-plus/basal-bolus arm (WMD -0.105, p =0.027). The combination therapy of insulin and GLP-1RA significantly reduced body weight than the placebo/insulin intensification (insulin up-titration)/GLP-1RA arm (WMD -1.894, p <0.001) and basal-plus/basal-bolus arm (WMD -3.6, p =0.001). Patients on combination therapy of insulin and GLP-1RA had a higher chance of achieving the HbA1c target than placebo/insulin intensification (insulin up-titration)/GLP1 RA arm (RR 1.964, p <0.001), but not than basal-plus/basal-bolus arm (RR 1.037, 95% CI 0.971 to 1.103). Regarding the proportion of patients with confirmed hypoglycemia, comparable rates were observed when compared between combination therapy and placebo/insulin intensification (insulin up-titration)/GLP-1RA (RR 0.94, 95% 0.84 - 1.04); however, it was statistically significant when compared combination therapy and basal-plus/basal-bolus (RR 0.63, p <0.001).

Comparison with previous studies and the significance of the study findings

HbA1c and body weight decreased by 0.44% and 3.22 kg in a meta-analysis of 15 RCTs that compared GLP-1RA plus basal insulin with other antidiabetic drugs without increasing hypoglycemia risk. [66] GLP-1RA and basal insulin, when used together, had comparable effects on decreasing HbA1c as the basal-bolus insulin regimen, with a 33% reduced risk of hypoglycemia and 5.66 kg less weight gain. [66] Based on data from 26 RCTs, Maiorino and colleagues found that basal insulin combined with GLP-1RA was more effective than other injectable antidiabetics in treating T2DM. Compared to other injectable treat-

ments, GLP-1RA with basal insulin reduced HbA1c by 0.47% greater, resulting in 1.[65]-fold higher proportions of patients meeting the 7.0% HbA1c criteria. While HbA1c reduction was not more remarkable with the combination treatment than basal-bolus insulin regimens, it showed a 34% reduced risk of hypoglycemia and 4.7 kg more weight loss. [67]

The short-acting GLP-1RA agents primarily affect postprandial glucose due to their capacity to decrease stomach emptying, which is closely associated with the activation of the GLP-1 receptor. Long-acting GLP-1RA agents, on the other hand, have a more prominent insulinotropic action, providing glycemic control by lowering fasting glucose and, as a result, hyperglycemia throughout the day. [68] The most common combination treatment regimen consists of basal insulin combined with a short-acting GLP-1RA or once-daily liraglutide, either as a separate ingredient preparation or a fixed ratio combination. Other new treatment plans include using a GLP-1RA injection once a week in addition to a single injection of a long-acting insulin analogue or numerous injections of a short-acting insulin analogue prior to meals. [49,52] When basal insulin fails to meet the fasting glucose goal, and improvements in fasting and postprandial glucose are needed, long-acting GLP1 RAs may be especially beneficial. One of the benefits of using GLP-1RAs once weekly is that additional daily injections beyond basal insulin are avoided. Type 2 diabetics who need to increase their insulin doses but do not want to increase their daily injections might benefit from adding a once-weekly GLP-1RA to meal-time insulin.[49,55]

A meta-analysis showed no significant differences in HbA1c change, the achievement of goal HbA1c, hypoglycemia risk, or bodyweight change when comparing each combination treatment method with the up-titration of basal insulin. [69] Moreover, in a real-world study, the decrease in HbA1c levels between free up-titration and the fixed-ratio combination was about the same. The free-up-titration group, on the other hand, used fewer insulin doses at the end of the study and lost more weight. In this investigation, the risk of hypoglycemia was not assessed. [70] A recently published article [71] showed that the efficiency of glycemic control was equivalent between free up-titration and fixed-ratio combination, which supports prior research that compared the two approaches. [69,70]

Strength points and limitations

This updated meta-analysis has many strength points. We conducted this meta-analysis in strict adherence to the PRISMA checklist, and we only included RCTs.

We compared the combination therapy with (a) placebo/insulin intensification (insulin up-titration)/GLP-1RA and (b) basal-plus/basal-bolus. We included a considerable number of the included studies through the end of 2021.

However, A few caveats must be taken into account, as well. The findings' generalizability may be limited due to the heterogeneity among the included studies and evidence of publication bias. Inherent characteristics of the studies included in this meta-analysis, such as patient characteristics, comparator medications, GLP-1RA doses, background treatment, and trial design, may explain the significant degree of heterogeneity. In addition, most studies were funded by industry, had short durations, and employed open-label designs to evaluate the long-term effects of the combination. To further understand the long-term effects, tolerance, and development of diabetic complications, more research is warranted.

Conclusion

Overall, our findings support the use of GLP-1RA in combination with insulin as a useful intensification approach for producing therapeutic improvement in type 2 diabetes therapy for individuals who have not reached their HbA1c goal. Compared to placebo insulin intensification (insulin up-titration)/GLP-1RA alone, the combination resulted in a higher decline in HbA1c levels, with more patients reaching the HbA1c target of 7%, weight loss, and a comparable risk of hypoglycemia. Moreover, the combination led to a higher decline in HbA1c, weight loss, lower risk of hypoglycemia, and a comparable proportion of patients reaching the HbA1c target of 7%.

Author's contributions

Dr. RA. was involved in study conceptualization, design, developing search strategy, data extraction, data analysis, and manuscript writing.

Dr. KKA is involved in data extraction and manuscript writing.

Dr. ASH is involved in manuscript writing and editorial support.

PROSPERO registry number

NA

Key Points

- GLP-1RA has multiple benefits in patients with T2DM, including improved insulin secretion, reduced food intake, and weight loss.
- This study aimed to compare the efficacy of GLP-1RA with other injectable therapies in patients with T2DM.
- Insulin and GLP-1RA combination therapy was found to be more effective in reducing HbA1c and body weight compared to placebo/insulin intensification (insulin up-titration)/GLP-1RA and basal-plus/basal-bolus therapies.
- Patients on insulin and GLP-1RA combination therapy had a higher chance of achieving the HbA1c target than those on placebo/insulin intensification (insulin up-titration)/GLP-1RA therapy.
- GLP-1RA in combination with insulin is a useful intensification approach for therapeutic improvement in T2DM therapy.

References

1. Ebada MA, Fayed N, Fayed L, Alkanj S, Abdelkarim A, Farwati H, et al. Efficacy of alpha-lipoic acid in the management of diabetes mellitus: A systematic review and meta-analysis. Iran J Pharm Res. 2019;18(4):2144–56.
2. Abdelhaleem IA, Salamah HM, Alsabbagh FA, Eid AM, Hussien HM, Mohamed NI, et al. Efficacy and safety of imeglimin in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized clinical trials. Diabetes Metab Syndr Clin Res Rev. 2021;15(6):102323.
3. Webber S. International Diabetes Federation. Vol. 102, Diabetes Research and Clinical Practice. 2013. p. 147–8.
4. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med. 2012;29(5):682–9.
5. Lipska KJ, Yao X, Herrin J, McCoy RG, Ross JS, Steinman MA, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. In: Diabetes Care. 2017. p. 468–75.
6. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: Real-world evidence in patients newly diagnosed with type 2 diabetes. Diabetes Care. 2018;41(1):69–78.
7. Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Ceriello A, Esposito K. Efficacy of insulin analogs in achieving the hemoglobin A 1c target of <7% in type 2 diabetes: Meta-analysis of randomized controlled trials. Diabetes Care. 2011;34(2):510–7.
8. Davies MJ, D'Alessio DA, Fradkin J,

Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the european association for the study of diabetes (EASD). Vol. 41, Diabetes Care. 2018. p. 2669–701.

9. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Vol. 17, Cell Metabolism. 2013. p. 819–37.

10. Aroda VR. A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. Vol. 20, Diabetes, Obesity and Metabolism. 2018. p. 22–33.

11. Gough SCL, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: Results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2(11):885–93.

12. Buse JB, Vilsboll T, Thurman J, Blevins TC, Langbakke IH, Bottcher SG, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care. 2014;37(11):2926–33.

13. S. L, B.W. B, L.B. C, J.-P. C, Y. H, L.M. L, et al. Efficacy and safety of IDegLira (combination of insulin degludec + liraglutide), in insulin-na{ï} ve patients with type 2 diabetes uncontrolled on GLP-1 receptor agonist (GLP-1RA) therapy. Diabetologia [Internet]. 2015;58(1):S401--S402. Available from: http://www.embase.com/search/results?subaction=viewrecord%7B&%7Dfrom=export%7B&%7Did=L72031078%5Cnhttp://dx.doi.org/10.1007/s00125-015-3687-4%5Cnhttp://zp9vv3zm2k.search.serialssolutions.com/?sid=EMBASE%7B&%7Disn=0012186X%7B&%7Did=doi:10.1007%7B%25%7D2Fs00125-015-3687-4%7B&%7Datitle=Ef

14. Lingvay I, Manghi FP, García-Hernández P, Norwood P, Lehmann L, Tarp-Johansen MJ, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL v randomized clinical trial. JAMA - J Am Med Assoc. 2016;315(9):898–907.

15. PHILIS-TSIMIKAS A, BILLINGS L, BUSCH RS, PORTILLO CM, SAHAY R, HALLADIN N, et al. Superior Ef-

ficacy of Insulin Degludec/Liraglutide (IDegLira) vs. Insulin Glargine (IGlar U100) as Add-On to Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i) ± Oral Antidiabetic Drug (OAD) Therapy in Patients with Type 2 Diabetes (T2D)—DUAL IX Trial. Diabetes. 2018;67(Supplement_1).

16. Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: The LixiLan-L randomized trial. In: Diabetes Care. 2016. p. 1972–80.

17. Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: The LixiLan-O randomized trial. In: Diabetes Care. 2016. p. 2026–35.

18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009 Oct;62(10):e1–34.

19. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8(1):16.

20. Kaku K, Araki E, Tanizawa Y, Ross Agner B, Nishida T, Ranthe M, et al. Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naïve Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial. Diabetes, Obes Metab. 2019;21(12):2674–83.

21. Pei Y, Agner BR, Luo B, Dong X, Li D, Liu J, et al. DUAL II China: Superior HbA1c reductions and weight loss with insulin degludec/liraglutide (IDegLira) versus insulin degludec in a randomized trial of Chinese people with type 2 diabetes inadequately controlled on basal insulin. Diabetes, Obes Metab. 2021;23(12):2687–96.

22. Rosenstock J, Nino A, Soffer J, Erskine L, Acusta A, Dole J, et al. Impact of a weekly glucagon-like peptide 1 receptor agonist, albiglutide, on glycemic control and on reducing prandial insu-

lin use in type 2 diabetes inadequately controlled on multiple insulin therapy: A randomized trial. Diabetes Care. 2020;43(10):2509–18.

23. Terauchi Y, Nakama T, Spranger R, Amano A, Inoue T, Niemoeller E. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi 1:1) in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs: A randomized, 26-week, open-label, multicentre study: The LixiLan JP-O2 randomized clinical trial. Diabetes, Obes Metab. 2020;22(S4):14–23.

24. Wang X, Zhang H, Zhang Q, Guan M, Sheng S, Mo W, et al. Exenatide and Renal Outcomes in Patients with Type 2 Diabetes and Diabetic Kidney Disease. Am J Nephrol. 2020;51(10):806–14.

25. Watada H, Kaneko S, Komatsu M, Agner BR, Nishida T, Ranthe M, et al. Superior HbA1c control with the fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with a maximum dose of 50 units of insulin degludec in Japanese individuals with type 2 diabetes in a phase 3, double-blind, randomized trial. Diabetes, Obes Metab. 2019;21(12):2694–703.

26. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AYM, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes. Ann Intern Med. 2011;154(2):103–12.

27. Devries JH, Bain SC, Rodbard HW, Seufert J, D'Alessio D, Thomsen AB, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes Care. 2012;35(7):1446–54.

28. Li C jun, Li J, Zhang Q mei, Lv L, Chen R, Lv C feng, et al. Efficacy and safety comparison between liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity. Cardiovasc Diabetol. 2012;11:1–8.

29. Seino Y, Min KW, Niemoeller E, Takami A, Abe N, Arai K, et al. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes, Obes Metab. 2012;14(10):910–7.

30. Riddle MC, Aronson R, Home P, Marre M, Niemoeller E, Miossec P, et al.

Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: A 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013;36(9):2489–96.

31. Riddle MC, Forst T, Aronson R, Sauque-Reyna L, Souhami E, Silvestre L, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: A 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care. 2013;36(9):2497–503.

32. De Wit HM, Vervoort GMM, Jansen HJ, De Grauw WJC, De Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: A 26 week, randomised clinical trial (ELEGANT). Diabetologia. 2014;57(9):1812–9.

33. Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: A randomized prospective trial. Diabetes, Obes Metab. 2014;16(9):827–32.

34. Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, de Loredo L, Tornøe K, et al. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial. Diabetes, Obes Metab. 2015;17(11):1056–64.

35. Lind M, Hirsch IB, Tuomilehto J, Dahlqvist S, Ahrén B, Torffvit O, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: Randomised clinical trial (MDI Liraglutide trial). BMJ. 2015;351:1–10.

36. Aroda VR, Bailey TS, Cariou B, Kumar S, Leiter LA, Raskin P, et al. Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 Study). Diabetes, Obes Metab. 2016 Jul;18(7):663–70.

37. Rosenstock J, Diamant M, Aroda VR, Silvestre L, Souhami E, Zhou T, et al. Efficacy and safety of Lixi Lan, a Titratable Fixed-Ratio Combination of Lixisenatide and Insulin Glargine, Versus Insulin Glargine in type 2 diabetes inadequately controlled on Metformin Monotherapy: The LixiLan proof-of-concept randomized trial. Diabetes Care. 2016;39(9):1579–86.

38. Seino Y, Kaneko S, Fukuda S, Osonoi

T, Shiraiwa T, Nishijima K, et al. Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: A 36-week, randomized, double-blind, parallel-group trial. J Diabetes Investig. 2016;7(4):565–73.

39. Vanderheiden A, Harrison L, Warshauer J, Li X, Adams-Huet B, Lingvay I. Effect of adding liraglutide vs placebo to a high-dose lnsulin regimen in patients with type 2 diabetes a randomized clinical trial. JAMA Intern Med. 2016;176(7):939–47.

40. Linjawi S, Bode BW, Chaykin LB, Courrèges JP, Handelsman Y, Lehmann LM, et al. The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial. Diabetes Ther. 2017;8(1):101–14.

41. Pozzilli P, Norwood P, Jódar E, Davies MJ, Ivanyi T, Jiang H, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes, Obes Metab. 2017 Jul;19(7):1024–31.

42. Guja C, Frías JP, Somogyi A, Jabbour S, Wang H, Hardy E, et al. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. Vol. 20, Diabetes, Obesity and Metabolism. 2018. 1602–1614 p.

43. Rodbard HW, Lingvay I, Reed J, De La Rosa R, Rose L, Sugimoto D, et al. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. J Clin Endocrinol Metab. 2018;103(6):2291–301.

44. Yang W, Min K, Zhou Z, Li L, Xu XJ, Zhu D, et al. Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: The GetGoal-L-C randomized trial. Diabetes, Obes Metab. 2018;20(2):335–43.

45. Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care. 2014;37(10):2763–73.

46. Mathieu C, Rodbard HW, Cariou B, Handelsman Y, Philis-Tsimikas A, Ocampo Francisco AM, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type

2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes, Obes Metab. 2014 Jul;16(7):636–44.

47. Rosenstock J, Fonseca VA, Gross JL, Ratner RE, Ahrén B, Chow FCC, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: A comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care. 2014;37(8):2317–25.

48. Shao N, Kuang HY, Hao M, Gao XY, Lin WJ, Zou W. Benefits of exenatide on obesity and non-alcoholic fatty liver disease with elevated liver enzymes in patients with type 2 diabetes. Diabetes Metab Res Rev. 2014 Sep;30(6):521–9.

49. Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): A randomised, open-label, phase 3, non-inferiority study. Lancet. 2015;385(9982):2057–66.

50. Probstfield JL, Hirsch IB, Davis BR, Ahmann A, Bergenstal R, Gilbert M, et al. Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus glp-1 agonist in participants with type 2 diabetes at high cardiovascular risk. Diabetes Care. 2016;39(6):973–81.

51. Rosenstock J, Guerci B, Hanefeld M, Gentile S, Aronson R, Tinahones FJ, et al. Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 Trial. Diabetes Care. 2016;39(8):1318–28.

52. Tonneijck L, Muskiet MHA, Smits MM, Hoekstra T, Kramer MHH, Danser AHJ, et al. Postprandial renal haemodynamic effect of lixisenatide vs once-daily insulin-glulisine in patients with type 2 diabetes on insulin-glargine: An 8-week, randomised, open-label trial. Diabetes, Obes Metab. 2017;19(12):1669–80.

53. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: The dual VII randomized clinical trial. Diabetes Care. 2018;41(5):1009–16.

54. Miya A, Nakamura A, Miyoshi H, Cho KY, Nagai S, Kurihara Y, et al. Satisfaction of switching to combination

therapy with lixisenatide and basal insulin in patients with type 2 diabetes receiving multiple daily insulin injection therapy: A randomized controlled trial. J Diabetes Investig. 2018;9(1):119–26.

55. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6(8):605–17.

56. Yamamoto S, Hayashi T, Ohara M, Goto S, Sato J, Nagaike H, et al. Comparison of liraglutide plus basal insulin and basal-bolus insulin therapy (BBIT) for glycemic control, body weight stability, and treatment satisfaction in patients treated using BBIT for type 2 diabetes without severe insulin deficiency: A randomized prospective pilot study. Diabetes Res Clin Pract. 2018;140:339–46.

57. Abreu M, Tumyan A, Elhassan A, Peicher K, Papacostea O, Dimachkie P, et al. A randomized trial comparing the efficacy and safety of treating patients with type 2 diabetes and highly elevated HbA1c levels with basal-bolus insulin or a glucagon-like peptide-1 receptor agonist plus basal-bolus insulin: The SIMPLE study. Diabetes, Obes Metab. 2019;21(9):2133–41.

58. Aroda VR, González-Galvez G, Grøn R, Halladin N, Haluzík M, Jermendy G, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7(8):596–605.

59. Aso Y, Takada Y, Tomotsune K, Chiba Y, Matsumura M, Jojima T, et al. Comparison of insulin degludec (IDeg)/insulin Aspart (IAsp) co-formulation therapy twice-daily with free combination of GLP-1 receptor agonist liraglutide plus insulin degludec in Tochigi: IDEAL Trial. Int J Clin Pract. 2021;75(4).

60. Billings LK, Agner BFR, Altuntas Y, Grøn R, Halladin N, Klonoff DC, et al. The Benefit of Insulin Degludec/Liraglutide (IDegLira) Compared With Basal-Bolus Insulin Therapy is Consistent Across Participant Subgroups With Type 2 Diabetes in the DUAL VII Randomized Trial. J Diabetes Sci Technol. 2020;15(3):636–45.

61. Giugliano D, Longo M, Caruso P, Di Fraia R, Scappaticcio L, Gicchino M,

et al. Feasibility of simplification from a basal-bolus insulin regimen to a fixed-ratio formulation of basal insulin plus a glp-1ra or to basal insulin plus an SGLT2 inhibitor: BEYOND, a randomized, pragmatic trial. Diabetes Care. 2021;44(6):1353–60.

62. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetesd2019. Diabetes Care. 2019 Jan;42(Supplement_1):S90–102.

63. Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. 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 Mar;51(3):417–28.

64. Maiorino MI, Bellastella G, Esposito K, Giugliano D. Premixed insulin regimens in type 2 diabetes: pros. Endocrine. 2017 Jan;55(1):45–50.

65. Maiorino MI, Chiodini P, Bellastella G, Scappaticcio L, Longo M, Giugliano D, et al. The good companions: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. A systematic review and meta-analysis of randomized controlled trials. Vol. 154, Diabetes Research and Clinical Practice. 2019. p. 101–15.

66. 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 Dec;384(9961):2228–34.

67. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Care. 2017 Apr;40(4):614–24.

68. Andersen A, Lund A, Knop FK, Vilsbøll T. Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol. 2018 Jul;14(7):390–403.

69. Maiorino MI, Chiodini P, Bellastella G, Scappaticcio L, Longo M, Esposito K, et al. Free and fixed-ratio combinations of basal insulin and GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes, Obes Metab. 2018 Sep;20(9):2309–13.

70. Morieri ML, Rigato M, Frison V, Simioni N, D'Ambrosio M, Tadiotto F, et al.

Fixed versus flexible combination of GLP-1 receptor agonists with basal insulin in type 2 diabetes: A retrospective multicentre comparative effectiveness study. Diabetes, Obes Metab. 2019 Nov;21(11):2542–52.

71. Jung HN, Cho YK, Min SH, Kim HS, Kim YJ, Park JY, et al. Free Versus Fixed-Ratio Combination of Basal Insulin and GLP-1 Receptor Agonists in Type 2 Diabetes Uncontrolled With GLP-1 Receptor Agonists: A Systematic Review and Indirect Treatment Comparison. Front Endocrinol (Lausanne). 2022 May;13.