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Review

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

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ABSTRACT

We provided an updated systematic review with meta-analysis of randomized controlled trials (RCTs) assessing the metabolic effects of combination therapy of insulin and GLP-1RA (combo) in comparison with other injectable therapy. We searched PubMed, Cochrane Register of Controlled Trials, Scholar, and ClinicalTrials.gov for RCTs evaluating changes in HbA1c (primary outcome), proportion of patients at HbA1c target <7%, hypoglycaemia, and weight change (secondary end-points). We included 36 RCTs involving 14,636 patients. Compared with comparator therapies (overall analysis), the combo led to a significant HbA1c reduction (=−0.49%, 95% CI −0.61 to −0.38%, P < 0.001), more patients at HbA1c target [relative risk, (RR) = 1.77, 95% CI, 1.56, 2.01, P < 0.001], similar hypoglycaemic events (RR = 1.03, 95% CI, 0.88, 1.19, P = 0.728), and reduction in body weight (−2.5 Kg, 95% CI −3.1 to −1.8 kg, P < 0.001), with high heterogeneity in each analysis. The quality of the evidence was low for three of the considered outcomes. Compared with intensified insulin regimens (basal-plus/basal-bolus) the combo produced similar glycemic control with reduction of both hypoglycaemia, and body weight. Combination therapy of GLP-1RA and insulin could represent a valuable treatment strategy to improve glycemic control in the management of type 2 diabetes.

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Contents

1. Introduction

Type 2 diabetes is a progressive disease which often requires treatment intensification to maintain adequate glucose control, due to the gradual decline of beta cells' function. Insulin therapy, usually started as a long-acting insulin analog at bedtime, is frequently needed after the failure of several oral glucose-lowering medications to reach and maintain HbA1c targets [1]. However, as emerged from both randomized controlled trials (RCTs) [2,3] or cohort studies [4,5], a significant proportion of patients assuming basal insulin therapy fail to achieve the desired glycemic goals. Recognizing that increasing basal insulin dose up to 0,5 UI/Kg does not result in further improvement of glycemic control, but raises the risk of weight gain and hypoglycemia [6], the American Diabetes Association's *Standard of Medical Care in Diabetes-2019* suggest to advance to a combination injectable therapy using a GLP-1 receptor agonist (GLP-1RA) or multiple doses of insulin [1].

The combination therapy of insulin and GLP-1 RAs rests on a compelling physiologic and clinical rationale, owing to the synergistic and complementary effects of its components [7,8]. GLP-1RAs enhance insulin secretion in a glucose-dependent manner, suppress glucagon, target post-prandial glucose by slowing gastric emptying, and promote weight loss, thus conferring glycemic control with a low risk of hypoglycaemia and weight gain. Therefore, GLP-1RAs offer an ideal companion to insulin, that addresses mainly fasting and post-absorptive glucose control, counterbalancing the adverse effects typically associated with insulin therapy [7,8].

Previous meta-analyses of RCTs [9,10] have shown that the insulin/GLP-1RA combination (combo) was associated with a mean reduction of HbA1c of around 0.45% as compared with other injectable treatment strategies, with no increased risk of hypoglycemia and significant reduction in body weight. These findings are in line with those coming from the expanding real world use of the combo strategies in type 2 diabetes [11–13].

The recent availability of RCTs that (a) evaluated the efficacy of weekly GLP-1RAs plus insulin, (b) compared the combo with complex insulin regimen (basal plus or full basal bolus), and (c) focused on different study populations may provide clinicians with new indications on safe and effective injectable treatment regimens to treat type 2 diabetes. We therefore did a systematic review and meta-analysis including RCTs published until March 2019 that compared the combo with other injectable therapy in patients with type 2 diabetes. In particular we sought to clarify: (1) whether the combo is similarly effective in reducing HbA1c when compared with its single components or basal plus/basal bolus insulin regimens; (2) whether the combo with short- and long- acting GLP-1RAs leads to the same glycemic outcomes; (3) whether the use of combo may produce additional benefits in terms of proportion of patients at HbA1c target < 7%, risk of hypoglycaemia, and weight change.

2. Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement [14]. The PRISMA checklist and the protocol of this study are reported in the Supplementary data. All data generated during this study are included in this published article and in the Supplementary file.

2.1. *Data sources and search strategy*

MEDLINE (via Pubmed), Cochrane Central Register of Controlled Trials, Google Scholar, and ClinicalTrials.gov (http://www.clinicaltrials.gov) databases were searched from data-

base inception to March 21, 2019. Our search strategy included the following keywords "insulin" or "biphasic insulin regimen" or "premixed insulin" or "basal-plus insulin regimen" or "basal-bolus insulin regimen", or "glargine" or "detemir" or "degludec" or "neutral protamine lispro" or "lispro" or "aspart" or "glulisine" and "glucagon-like peptide 1 receptor agonist" or "GLP-1" or "exenatide" or "exenatide LAR" or " liraglutide" or "lixisenatide" or "dulaglutide" or "albiglutide" or "semaglutide" or "IDegLira" or "IGlarLixi" or "fixed combination of GLP-1 receptor agonist and insulin". The complete PubMed search was described in Supplementary Table 1. We also did a manual search, using the reference list of prior reviews and meta-analyses.

2.2. Study selection

We considered studies eligible for inclusion if they were RCTs conducted on adults with type 2 diabetes, compared both free or fixed combo of short- and long-acting GLP-1RAs and insulin with other injectable treatment strategy, had at least a duration of 8 weeks, and reported changes in HbA1c and/or the proportion of participants with HbA1c of <7.0% at the end of the study period or the number of participants with hypoglycemic events or weight change. Trials performed in type 2 diabetic patients with comorbidities including cardiovascular diseases or renal failure were also included. Two investigators (M.I.M. and D.G.) independently reviewed articles for eligibility on the basis of the study titles and abstracts, and studies that met the inclusion criteria were retrieved for full-text assessment. All disagreements were resolved by consensus.

2.3. Data extraction

Data extraction was performed by two investigators using a standardized tool, and discrepancies were resolved by consensus. For each retrieved study, we extracted the following data: (1) author identification and year of publication with trial name; (2) study design; (3) duration of intervention; (4) investigational drug with number of patients; (5) comparator drug with number of patients; (6) age and baseline levels of HbA1c; (7) background therapy in both study groups; (8) primary outcome; (9) HbA1c and weight change; (10) safety (hypoglycemia); (11) study funder; and (12) type of statistical analysis for the HbA1c outcome.

2.4. Risk of bias assessment

A risk assessment of bias was performed for each included RCT using the Cochrane Collaboration's tool [15]. We assessed risk of bias in random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The risks of bias were categorized a high, low, and unclear, and represented in a "Risk-of-Bias" graph. The quality of each RCT was assessed by one reviewer and verified by another reviewer. Disagreement was resolved by consensus.

2.5. Quality of evidence

We assessed the overall quality of evidence using the GRADE approach according to the Cochrane Handbook for Systematic Reviews of Interventions [15]. For each specific outcome, the quality of evidence was based on 5 factors: (1) limitations of the study design; (2) consistency of results; (3) directness; (4) precision and (5) potential for publication bias. We downgraded a starting rating of "high quality" evidence by one level for serious concerns (or by two levels for very serious concerns) about risk of bias, inconsistency, indirectness, imprecision or publication bias. The GRADE approach resulted in 4 levels of quality of evidence: high, moderate, low and very low [16].

2.6. Statistical analysis

The decrease of HbA1c from baseline at the end of treatment was the primary outcome of this meta-analysis. Secondary endpoints were proportion of patients at HbA1c target $\leq$ 7% (53 mmol/mol), incidence of hypoglycemic events, and weight change. Changes from baseline in HbA1c and body weight were analyzed as continuous variables, using weighted mean differences (WMDs) as summary measure. From each study, the difference between the two groups of the mean decrease of the continuous variable and its standard deviation was extracted. If not reported, standard deviation of the difference was estimated by standard equations from the reported standard error, confidence interval, or P value. Risk ratios (RRs) were used as the meta-analytic measure of association for patients at HbA1c targets < 7.0% (53 mmol/mol) and for incidence of hypoglycemic events. For each study, proportion of participants achieving an HbA1c of 7.0% (53 mmol/mol) or lower and those having any episode of hypoglycemia were used to calculate RR using 2x2 table. For studies with three groups and a shared intervention group, to include each pair-wise comparison separately, the shared group was split into two groups with sample size halved. Heterogeneity between studies was assessed by using Q statistic and I^2, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. $I^2 < 25\%$ was considered as low in heterogeneity, $I^2 > 75\%$ as high in heterogeneity, a P value of Q statistic less than 0.10 was considered significant [15]. If overall heterogeneity was significant, a random-effect model was used, otherwise a fixed-effect model was used. In a conservative way, we considered random-effect analysis the main focus of our meta-analysis. We did preplanned subgroup analyses restricted to trials that compared combination vs placebo/insulin intensification/GLP-1RA; combination vs basal-plus/basal-bolus; and short- vs long-acting. Publication bias was assessed visually with funnel plots and with Egger test [17]; a P value of less than 0.10 was considered significant. The trim-and-fill method was used to estimate the effect of publication bias [18]. Sensitivity analyses in which each study was removed in turn to assess the influence of that study on the overall effect size were also carried out. For descriptive purposes, median and interquartile range (IQR) were calculated for continuous variables in the two groups. Data were

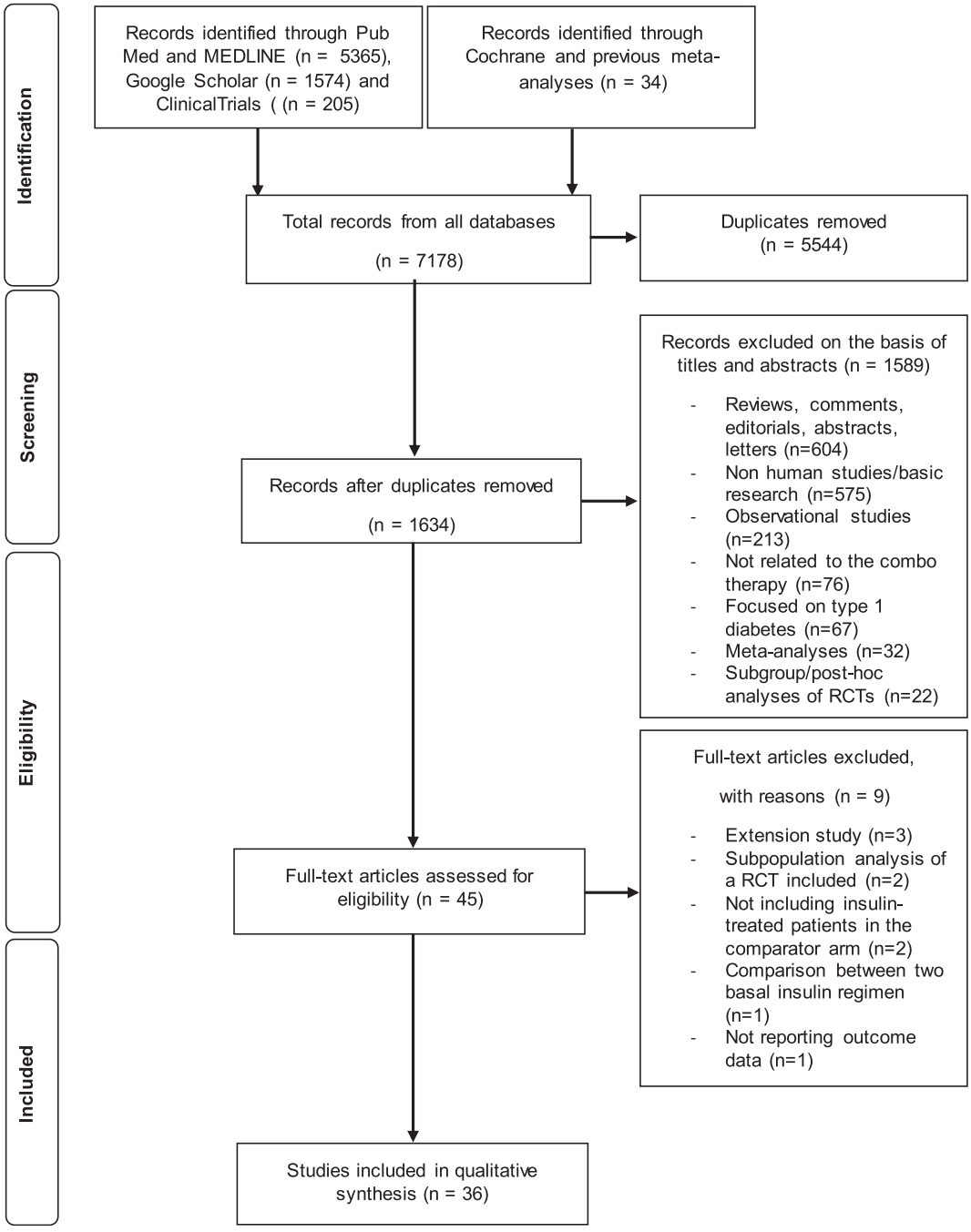

Fig. 1 – Process of studies' selection.

analyzed using Stata, version 11.2 (Stata Corp., College Station, TX). All statistical tests were two sided, and P values < 0.05 were regarded significant.

3. Results

3.1. *Search results and study characteristics*

The flow diagram documenting the process of study selection is reported in Fig. 1. The initial search retrieved 7178 records, of whom 1634 abstracts were selected for review, after removing duplicates. We then excluded 1589 citations on the basis of title and abstracts (mostly reviews, observational and pre-clinical studies). Of the remaining 45 RCTs, 9 were excluded because they were extension studies (n = 3), subgroup analysis of a RCT included (n = 2), not included insulin-treated patients (n = 2), compared two basal insulin regimen (n = 1), or not reported outcome data (n = 1) (Supplementary Table 2). Finally 36 RCTs [19–54] with 42 comparisons were included for quantitative synthesis and meta-analysis.

The characteristics of the included RCTs with baseline patients' features are presented in Table 1. The trials were published between 2011 and 2018, with 7 trials [40–42,51–54] published in 2018. Most RCTs were multinational and

Table 1 – Characteristics of RCTs included in the meta-analysis.

Author, year (trial name)	Study design	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Background therapy	Primary outcome
Buse et al. (2011)	DB	30	Exenatide 10 μg BID	138	59 (9)	8.3 (0.8)	Glargine ± metformin, pioglitazone, or both	HbA1c levels at week 30
			Placebo	123	59 (10)	8.5 (0.9)		
DeVries et al. (2012)	O	26	Detemir	162	56.8 (9.4)	7.6 (0.6)	Metformin + liraglutide	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)	O	12	Liraglutide 1.2 mg	42	51.2 (10.5)	8.8 (0.8)	Basal insulin or pre-mixed insulin ± metformin, sulphonilurea, thiazolidinedion, glinide, or α - glucosidase inhibitor	HbA1c levels at week 12
			Insulin up-titration	42	52.7 (10.8)	8.7 (0.9)		
Seino et al. (2012) *(Get-Goal-L-Asia)*	DB	24	Lixisenatide 20 μg	154	58.7 (10.2)	8.5 (0.7)	Basal insulin ± sulfonylurea	Change in HbA1c to week 24
			Placebo	157	58.0 (10.1)	8.5 (0.8)		
Riddle et al. (2013) *(Get-Goal-L)*	DB	24	Lixisenatide 20 μg	328	57 (10)	8.4 (0.9)	Basal insulin ± metformin	Change in HbA1c to week 24
			Placebo	167	57 (10)	8.4 (0.8)		
Riddle et al. (2013) *(GetGoal-Duo 1)*	DB	24	Lixisenatide 20 μg	223	56 (10)	7.6 (0.5)	Glargine plus metformin, ± pioglitazone	Change in HbA1c to week 24
			Placebo	223	56 (10)	7.6 (0.5)		
Buse et al. (2014) *(DUAL II)*	DB	26	IDegLira + Metformin	207	57 (9)	8.7 (0.7)	Basal insulin + metformin with or without sulphonilurea/glinide	Change in HbA1c to week 26
			Degludec + Metformin titration	206	58 (11)	8.8 (0.7)		
de Wit et al. (2014) *(ELEGANT)*	O	26	Liraglutide 1.8 mg	26	57 (10)	7.2 (0.6)	Basal insulin ± bolus insulin or metformin, sulphonilurea, or both	Change in body weight to week 26
			Intensification of insulin therapy	24	59 (8)	7.5 (0.7)		
Gough et al. (2014) *(DUAL-I)*	O	26	IDegLira	834	55.1 (9.9)	8.3 (0.9)	Metformin ± pioglitazone	Change in HbA1c to week 26
			Degludec	414	54.9 (9.7)	8.3 (1.0)		
			Liraglutide 1.8 mg	415	55.0 (10.2)	8.3 (0.9)		

(*continued in next page*)

Table 1 – (*continued*)

Author, year (trial name)	Study design	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Background therapy	Primary outcome
Lane et al. (2014)	O	24	Liraglutide 1.8 mg	21	59 (11.8)	7.8 (0.6)	CSII or MDI ± metformin	HbA1c at week 24
			Insulin up-titration	16	60.8 (9.7)	7.8 (0.7)		
Ahmann et al. (2015) *(LIRA-ADD2BASAL)*	DB	26	Liraglutide 1.8 mg	226	59.3 (9.2)	8.2 (0.8)	Basal insulin ± metformin	Change in HbA1c to week 26
			Placebo	225	57.5 (11.1)	8.3 (0.9)		
Lind et al. (2015) *(MDI Liraglutide trial)*	DB	24	Liraglutide 1.8 mg	64	63.8 (8.2)	9.0 (1.0)	MDI ± metformin	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)*	DB	26	Degludec	174	57 (10)	7.6 (0.6)	Metformin + liraglutide	Change in HbA1c to week 26
			Placebo	172	57.3 (9.4)	7.6 (0.6)		
Aroda et al. (2016) *(LixiLan-L)*	O	30	IGlarLixi	367	59.6 (9.4)	8.1 (0.7)	Glargine + metformin	Change in HbA1c to week 30
			Glargine titration	369	60.3 (8.7)	8.1 (0.7)		
Lingvay et al. (2016) *(DUAL V)*	O	26	IDegLira	278	58.4 (9.8)	8.4 (0.9)	Glargine + metformin	Change in HbA1c to week 26
			Glargine titration	279	59.1 (9.3)	8.2 (0.9)		
Rosenstock et al. (2016) *(Lixilan PoC)*	O	24	IGlarLixi	161	56.9 (9.5)	8.1 (0.8)	Metformin	Change in HbA1c to week 24
			Glargine titration	162	56.6 (9.4)	8.0 (0.8)		
Rosenstock et al. (2016) *(LixiLan-O)*	O	30	IGlarLixi	469	58.2 (9.5)	8.1 (0.7)	Metformin	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)		
Seino et al. (2016)	DB	36	Liraglutide 0.9 mg	127	61.3 (11)	8.8 (0.9)	Basal or premixed or basal bolus therapy	Change in HbA1c to week 16
			Placebo	130	59.8 (11.3)	8.8 (0.9)		
Vanderheiden et al. (2016)	DB	24	Liraglutide 1.8 mg	35	52.8 (8.1)	9.0 (1.2)	High dose insulin regimen	Change in HbA1c to week 24
			Placebo	36	55.5 (6.6)	8.9 (1.0)		
Linjawi et al. (2017) *(DUAL III)*	O	26	IDegLira	292	58.3 (9.9)	7.8 (0.6)	Metformin and/or pioglitazone ± sulfonylurea	Change in HbA1c to week 26
			Liraglutide or Exenatide at their pre-trial dose	146	58.4 (8.8)	7.7 (0.6)		
Pozzilli et al. (2017) *(AWARD-9)*	DB	28	Dulaglutide 1.5 mg	150	60.2 (9.5)	8.4 (0.9)	Glargine ± metformin	Change in HbA1c to week 28
			Placebo	150	60.6 (10.1)	8.3 (0.8)		

Guja et al. (2018) *(DURATION-7)*	DB	28	Exenatide LAR 2 mg	231	57.8 (9)	8.5 (0.9)	Glargine ± metformin	Change in HbA1c to week 28
			Placebo	230	57.6 (10.3)	8.5 (0.9)		
Rodbard et al. (2018) *(SUSTAIN-5)*	DB	30	Semaglutide 0.5 mg	132	59.1	8.4	Basal insulin ± metformin	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)*	DB	24	Lixisenatide 20 μg	224	53.9 (9.9)	7.9 (0.6)	Basal insulin ± metformin	Change in HbA1c to week 24
			Placebo	224	56.2 (9.1)	7.9 (0.7)		
Diamant et al. (2014) *(4B Study)*	O	30	Exenatide 10 μg BID	315	59.8 (9.5)	8.3 (1.0)	Glargine + metformin	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)*	O	26	Liraglutide 1.8 mg	88	61.1 (9.5)	7.7 (0.6)	Degludec + metformin	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)*	O	26	Albiglutide 30 mg	282	54.8 (9.1)	8.5 (0.9)	Glargine ± metformin, pioglitazone, or both	Change in HbA1c to week 26
			Lispro thrice daily	281	56.3 (8.9)	8.4 (0.9)		
Shao et al. (2014)	O	12	Exenatide 10 μg BID	30	43 (4.1)	7.6 (0.6)	Glargine	HbA1c at week 12
			Aspart thrice daily	30	42 (3.2)	7.7 (0.6)		
Blonde et al. (2015) *(AWARD-4)*	O	52	Dulaglutide 1.5 mg	295	58.9 (9.6)	8.5 (1.1)	Prandial lispro ± metformin	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)	O	26	Exenatide 5–10 μg	52	62	7.9 (0.3)	Glargine + metformin	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)*	O	26	Lixisenatide 20 μg	298	59.8 (8.6)	7.8 (0.6)	Glargine ± metformin	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)	O	8	Lixisenatide 20 μg	17	62 (7)	8.3 (0.2)	Glargine ± metformin	Change in GFR and ERPF to week 8
			Glulisine once daily	18	61 (7)	7.8 (0.2)		

(*continued in next page*)

Table 1 – (*continued*)

Author, year (trial name)	Study design	Study duration (week)	Study arms	Number of patients	Mean age (SD) (year)	Baseline HbA1c (SD) (%)	Background therapy	Primary outcome
Billings et al. (2018) *(DUAL VII)*	O	32	IDegLira	25,2	58.6 (9.0)	8.2 (0.8)	Glargine + metformin	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)	O	12	Lixisenatide 20 μg plus insulin glargine	11	66 (8.4)	7.1 (0.5)	MDI ± oral hypoglycemic agents	Change in the Diabetes Treatment Satisfaction Questionnaire scores to week 12
			Continuing MDI	15	59.6 (12.8)	7.2 (0.9)		
Tuttle et al. (2018) *(AWARD-7)*	O	52	Dulaglutide 1.5 mg	192	64.7 (8.8)	8.6 (0.9)	Prandial lispro	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)	O	24	Liraglutide 0.9 mg and basal insulin	13	60.0 (7.8)	7.3 (1.2)	Basal bolus insulin therapy	Change in HbA1c to week 24
			Continuing basal bolus insulin therapy	12	61.5 (10.6)	6.9 (0.8)		

CSII, continuous subcutaneous insulin infusion; DB, double blind; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; MDI, multiple daily injections of insulin; NS, not specified; O, open; RCTs, randomized controlled trials

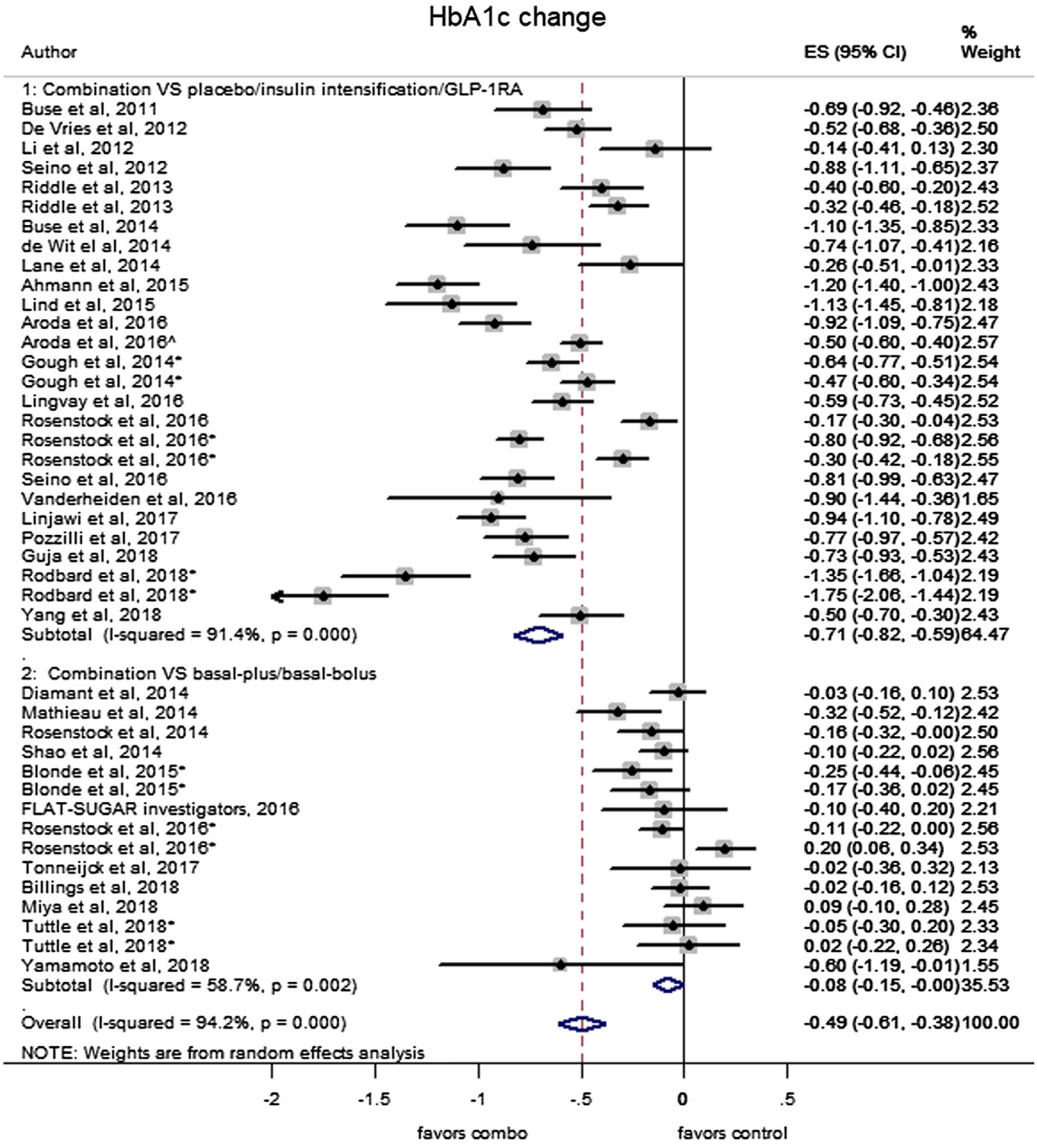

Fig. 2 – Forest plots of meta-analysis for HbA1c change from baseline in all 42 comparisons. There are 27 comparisons of combo vs placebo/insulin intensification/GLP-1RA, and 15 comparisons of combo versus basal-plus/basal-bolus. The results are expressed as WMD (HbA1c decrease in the combo arms minus HbA1c decrease in the comparator arms). Effect size (ES) < 0 favours combo; ES > 0 favours comparator therapy. For each estimate, the grey shaded area is the weight of the estimate in proportion to the overall effect.

received industry funding [19–27,29–45,47–52]; six studies [21,22,36,46,53,54] focused on Asian population. All trials were of parallel-group design, 14 were double-blind [19,22–25,29–31,36–37,39–42] and the remaining utilised an open-label design. The trials had a duration ranging from 8 to 52 weeks.

Trials' design were different: 24 trials, with 27 comparisons, compared the combo with placebo [19–20,22–24,29–31,36–37,39–42] or insulin intensification [21,25–28,32–35] or GLP-1RA alone [38] on a background of basal insulin therapy; 12 trials, with 15 comparisons, compared the combo with a basal plus insulin regimen (one injection of basal insulin plus one injection of a rapid acting analog at the largest meal) [44,49,50] or with a basal bolus insulin regimen (one injection of basal insulin plus three injections of a rapid acting analog before meals) [43–49,51–54]. Fourteen trials [19,22–24,32,34,35,42,43,46,48–50,53], with 16 comparisons, used a short-acting GLP-1RA (4 exenatide, and 10 lixisenatide), and 22 trials [20,21,25–31,33,36–41,44,45,47,51,52,54], with 26 comparisons,

Table 2 – Pre-planned subgroup analysis

Parameter	Comparisons	Patients	Controls	Estimate (95% CI)	*p*-value	I^2	*p*-value of Q test
HbA1c (%)				**WMD**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	27	5196	4965	−0.71 (−0.82, −0.59)	<0.001	91.4	<0.001
Vs Basal-plus/Basal-bolus	15	2328	2147	−0.08 (−0.15, −0.01)	0.038	58.7	0.002
Combo with short-acting GLP-1RA	16	2786	3147	−0.29 (−0.44, −0.14)	<0.001	93.7	<0.001
Combo with long-acting GLP-1RA	26	4738	3965	−0.63 (−0.78, −0.47)	<0.001	93.3	<0.001
All trials	42	7524	7112	−0.49 (−0.61, −0.38)	<0.001	94.2	<0.001
HbA1c < 7%				**RR**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	27	5196	4965	2.23 (1.88, 2.65)	<0.001	93.5	<0.001
Vs Basal-plus/Basal-bolus	10	2205	2022	1.07 (0.99, 1.15)	0.077	15.3	0.302
Combo with short-acting GLP-1RA	12	2676	3034	1.57 (1.28, 1.93)	<0.001	92.4	<0.001
Combo with long-acting GLP-1RA	25	4725	3953	1.91 (1.61, 2.27)	<0.001	92.1	<0.001
All trials	37	7401	6987	1.77 (1.56, 2.01)	<0.001	92.1	<0.001
Hypoglycemia				**RR**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	25	5111	4889	1.26 (1.06, 1.49)	0.008	82.2	<0.001
Vs Basal-plus/Basal-bolus	10	1628	1735	0.64 (0.52, 0.79)	<0.001	82.0	<0.001
Combo with short-acting GLP-1RA	15	2775	3132	1.02 (0.81, 1.28)	0.866	84.8	<0.001
Combo with long-acting GLP-1RA	20	3964	3492	1.04 (0.85, 1.27)	0.733	87.6	<0.001
All trials	35	6739	6624	1.03 (0.88, 1.19)	0.728	86.4	<0.001
Weight (Kg)				**WMD**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	26	5022	4793	−1.8 (−2.6, −1.1)	<0.001	97.1	<0.001
Vs Basal-plus/Basal-bolus	15	2328	2147	−3.6 (−4.5, −2.7)	<0.001	92.5	<0.001
Combo with short-acting GLP-1RA	16	2786	3147	−2.2 (−3.1, −1.4)	<0.001	96.0	<0.001
Combo with long-acting GLP-1RA	25	4564	3793	−2.7 (−3.6, −1.7)	<0.001	97.2	<0.001
All trials	41	7350	6940	−2.5 (−3.1, −1.8)	<0.001	96.8	<0.001

RR, relative risk; WMD, weighted mean difference.

used a long-acting GLP-1RA (16 liraglutide, 3 dulaglutide, 1 albiglutide, 1 exenatide LAR, and 1 semaglutide). Eight trials [25,27,32–35,38,52], with 9 comparisons, used a fixed ratio combination of GLP-1RA and insulin (5 IDegLira, and the remaining 3 IGlarLixi). Except for 4 trials [26,48,50,53], the primary outcome of the included studies was change in HbA1c to the end of trial.

The participants in all trials were adults (>18 years old) with type 2 diabetes; only one study [51] included patients with moderate-severe kidney disease. Mean patients' age ranged from 42 to 66 years, and mean baseline HbA1c levels ranged from 6.9% to 9.0%, with a median of 8.3% (IQR 7.8–8.5%) in the intervention groups and 8.2% (IQR 7.7–8.5%) in the comparator groups.

3.2. *Intervention*

All the RCTs evaluated a total of 14,636 type 2 diabetic patients for the primary outcome of this meta-analysis (change in HbA1c at the end of trial), 7524 in the intervention groups and 7112 in the comparator groups. Six trials [19,20,23,36,39,41] tested the superiority of the combo over placebo, eight trials [22,24,29,30,31,37,40,42] compared the combo with placebo, three trials [21,26,28] compared the combo with insulin intensification; four trials [43,47,49,51] tested the non inferiority of the combo, one trial [54] tested the superiority, and six trials [44–46,48,50,53] compared the combo with intensified insulin regimens (basal plus or basal bolus). Two trials [25,38] tested the superiority, and six trials [27,32,33,34,35,52] tested the non inferiority of the fixed ratio combination of GLP-1RA and insulin over basal insulin intensification or GLP-1RA alone or basal bolus therapy.

3.3. *Risk of bias*

According to the Cochrane Collaboration's tool for assessing risk of bias, selection bias was evaluated as unclear in all trials for allocation concealment; performance bias was evaluated as high in 22 trials for blinding of participants and personnel; detection bias was evaluated as high in 22 trials and unclear in 13 trials for blinding of outcome assessment (Supplementary Fig. 1, Supplementary Table 3).

3.4. *Outcomes*

In the meta-analysis of 42 comparisons for HbA1c change, the combo was associated with a significant 0.49% mean reduction (95% CI −0.61 to −0.38%, P < 0.001) compared with other injectable therapy, with high heterogeneity between studies (I^2 = 94.2%, P < 0.001) (Fig. 2, Table 2), and no evidence of publication bias (Egger test, P = 0.078). Based on the GRADE approach, the quality of the evidence for this outcome was considered moderate due to the inconsistency of the results in this analysis (Supplementary Table 5). Pre-planned subgroup analysis showed that the greatest reduction in HbA1c levels was obtained when the combo was compared with pla-

cebo/insulin intensification/GLP-1RA (27 comparisons, −0.71%, 95% CI −0.82 to −0.59%, P < 0.001) (Fig. 2, Table 2). The mean reduction of HbA1c ranged from −0.84% in the comparisons of combo with placebo, to −0.46% in the comparisons of combo with insulin intensification; heterogeneity was high in all subgroup analyses (Supplementary Table 4). In the 15 comparisons between the combo versus basal-plus/basal-bolus, the difference for HbA1c was lowest (-0.08%, 95% CI, −0.15% to −0.01, P = 0.038), with heterogeneity (I^2 = 58.7%, P < 0.001) (Fig. 2, Table 2). The mean reduction of HbA1c was −0.29% for combo with short-acting GLP-1RA, and −0.63% for combo with long-acting GLP1-RA; heterogeneity remained high in both subgroup analyses (Table 2).

The overall analysis of 37 comparisons that evaluated the proportion of patients achieving an HbA1c target < 7% at the end of intervention showed a 77% higher likelihood of reaching this glycemic goal in patients using the combo, as compared with those using other injectable treatment (RR = 1.77, 95% CI 1.56–2.01, P < 0.001), with high heterogeneity (I^2 = 92.1%, P < 0.001), and evidence of publication bias (Egger test, P < 0.001) (Table 2, Supplementary Fig. 2). The trim-and-fill method indicated that this publication bias minimally reduced the estimate (1.35, 95%CI 1.18–1.54), without changing its statistical significance (P < 0.001). Based on the GRADE approach, the overall quality of evidence was low (due to the inconsistency of the results, publication bias and some imprecision of the results) (Supplementary Table 5). The likelihood to reach the HbA1c was highest when the combo was compared with placebo/insulin intensification/GLP-1RA (RR = 2.23, 95% CI 1.88, 2.65, P < 0.001), whereas no difference was found between the combo versus basal-plus/basal-bolus (RR = 1.07, 95% CI 0.99, 1.15, P = 0.302) (Table 2, Supplementary Fig. 2). As expected, the RR relative to HbA1c target < 7% was highest when the combo was compared with placebo (RR = 3.34, 95%CI 2.51, 4.45, P < 0.001) and lowest when the combo was compared to insulin intensification (RR = 1.44, 95% CI 1.21, 1.72, P < 0.001); heterogeneity was high in all subgroup analyses (Supplementary Table 4). Compared with control subjects, patients using short- or long-acting GLP-1RA showed a 57% and 91% increase in likelihood of achieving the HbA1c target, respectively (Table 2). Heterogeneity was high in all subgroups analysis, except for the 10 comparisons between the combo versus complex insulin regimen (basal plus or basal bolus) (Table 2).

The overall analysis of 35 comparisons that assessed the risk of any hypoglycemic events during treatment showed no significant difference in the RR of hypoglycemia when the combo was compared with other injectable treatment (RR = 1.03, 95% CI 0.88, 1.19, P = 0.728) (Table 2, Supplementary Fig. 3), with high heterogeneity (I^2 = 86.4%, P < 0.001), and evidence of publication bias (Egger test, P = 0.031). At the trim-and-fill test, this publication bias did not change the statistical significance of the estimate (0.87, 95% CI 0.74–1.02). Based on the GRADE approach, the overall quality of evidence was low (due to the inconsistency of the results, publication bias and some imprecision of the results) (Supplementary Table 5). There was a significant 26% increase in the RR of hypoglycemia when the combo was compared with placebo/insulin intensification/GLP-1RA (RR 1.26, 95% CI 1.06, 1.49, P = 0.008), which was highest in the comparisons between the combo and placebo (RR 1.33, 95% CI 1.12, 1.58, P = 0.001) (Supplementary Table 4), whereas a significant lower risk of 36% was found when the combo was compared with intensified insulin regimen (RR 0.64, 95% CI 0.52, 0.79, P < 0.001) (Table 2, Supplementary Fig. 3). No significant difference in the risk of hypoglycaemia was found with the use of short- or long-GLP-1RA, compared with their respective control arms. Heterogeneity was high for all subgroup comparisons (Table 2, Supplementary Fig. 3).

In the overall analysis of 41 comparisons, the combo led to a greater weight reduction, as compared with control treatment regimens (−2.5 Kg, 95% CI −3.1 to −1.8 Kg, P < 0.001) (Table 2, Supplementary Fig. 4), with high heterogeneity (I^2 = 96.8%, P < 0.001), and evidence of publication bias (Egger test, P = 0.001); the trim and fill method indicated that this publication bias did not change the estimate. Based on the GRADE approach, the overall quality of evidence was low (due to the inconsistency of the results and suspected publication bias) (Supplementary Table 5). The highest decrease in the mean difference of body weight was observed when the combo was compared with basal-plus/basal-bolus insulin regimens (−3.6 kg, 95% CI −4.5 to −2.7 kg, P < 0.001), and the lowest decrease was observed between the combo versus placebo/insulin intensification/GLP-1RA (−1.8 Kg, 95% CI −2.6 to −1.1, P < 0.001) (Table 2, Supplementary Fig. 4). Compared with GLP-1RA, the combo led to a mean body weight increase of 2.4 Kg (P < 0.001) (Supplementary Table S4). Moreover, both short- and long- GLP-1RAs produced a similar reduction of body weight (−2.2 kg and −2.7 kg, respectively). Heterogeneity was high for all subgroup comparison (Table 2).

4. Discussion

To our knowledge, this meta-analysis represents the most completed and up to date analysis of RCTs involving 14,636 type 2 diabetic patients. The combination therapy of insulin and GLP-1RA significantly improved glycemic control in terms of HbA1c reduction and number of patients at target (HbA1c < 7%), with weight loss and similar hypoglycemic risk compared with other injectable therapy, although these findings are influenced by a low quality of evidence for most of the considered outcomes. Specifically, the combo led to a higher reduction in HbA1c, with more patients at HbA1c target of 7%, higher risk of hypoglycemia and reduction in weight when compared to placebo, insulin up-titration or GLP-RA alone, and was as effective as insulin regimens, with less hypoglycemia and reduction in weight. In the past two years, ten new studies comparing the addition of a GLP-1RA to insulin versus alternative injectable therapy have been published [38–42,50–54]; among these, five studies evaluated the effects of the combo in comparison with GLP-1RA alone [38] or basal insulin up-titration [39–41], or placebo after optimization of basal insulin therapy [42]; the remaining five studies compared the combo with a basal plus [50] or a basal bolus insulin regimen [51–54]. The inclusion of these trials in the qualitative synthesis with additional 3211 patients led to results similar to those coming from our previous meta-analysis [10]. However, based on the low quality of the collected evidence, our confidence in the effect estimate is lim-

ited: the true effect may be substantially different from the estimate of the effect. The better metabolic effects provided by the combo in comparison with placebo or the intensification of its single components (mainly insulin up-titration) was not surprising; however, the combo led to a similar level of glycemic control than that offered by intensified regimens of insulin therapy (basal plus or basal bolus), with a lower risk of hypoglycemia (−36%) and weight loss (−3.6 Kg). Globally, our results support the role of GLP-1RA combined with insulin as a valuable intensification strategy to produce clinical benefit in the management of type 2 diabetes. Interestingly, the updated Consensus Report by the American Diabetes Association and the European Association for the Study of Diabetes suggest to intensify treatment with GLP-1RA, among other drugs including SGLT-2 inhibitors or prandial insulin, in patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications [55].

Due to the progressive nature of the disease, many patients with type 2 diabetes require insulin to reach their glycemic target. A common approach to start insulin therapy is a single injection of a basal insulin, eventually up-titrated to optimize treatment [1]. If needed, further intensification of insulin therapy to achieve glycemic goals may include the addition of one or more doses of premeal rapid-acting insulin analogues to ongoing basal insulin (basal plus or basal bolus, respectively), or switching to a premixed insulin regimen, in which there is a fixed amount of intermediate-acting and short- or rapid-acting insulin. Although these intensified insulin regimens lead to similar decrease in HbA1c levels [56,57], some reluctance to intensify insulin therapy often exists, due to potential adverse effects (i.e., increased hypoglycemia and weight gain) and practical concerns (i.e., patient anxiety about insulin, difficulties in educating patients about injection therapy). In this context, adding GLP-1RA to insulin may provide a novel and valid therapeutic option to improve glycemic control minimizing the adverse events associated with insulin intensification.

GLP-1RAs that received the U.S. Food and Drug Administration approval for use in combination with insulin include the short-acting exenatide and lixisenatide, and the long-acting liraglutide, exenatide extended release, albiglutide, dulaglutide, and semaglutide; except for liraglutide, all the long-acting GLP-1RAs are administered once weekly due to their prolonged half-life (from 90 h to several days). Moreover, there are currently two approved combination products containing fixed doses of long-acting insulins and GLP-1RA (fixed-ratio combo): IDegLira, a combination of insulin degludec (IDeg) and the long-acting GLP-1 analog liraglutide, and iGlarLixi, a combination of insulin glargine (IGlar) and the short-acting GLP-1RA lixisenatide [58]. The short acting compounds exert their effects predominantly on post-prandial glucose, according to their ability in slowing gastric emptying, that is strictly correlated with the phasic activation of the GLP-1 receptor [59]. On the other hand, long-acting GLP-1RAs, which activate the GLP-1 receptor continuously, show a more pronounced insulinotropic effect, providing glycemic control by reducing fasting glucose and, consequently, hyperglycemia during the entire day [59]. In the subgroup analysis comparing the combo with short-acting GLP-1RAs and long-acting GLP-1RAs, we observed a 0.29% and 0.63% decrease in HbA1c with short- and long-acting GLP-1RAs, respectively, with a similar weight loss (−2.2 Kg and −2.7 Kg). These results are in line with the expected overall effects provided by both short- and long-acting GLP-1RAs. Moreover, other variables influencing glycemic control include difference in baseline HbA1c levels, previous use of other oral agents, different definitions of hypoglycemia, presence or absence of run-in period, and the different duration of the trials. In an indirect comparison of the relative treatment effects between IDegLira and IGlarLixi in type 2 diabetic patients not well controlled on basal insulin therapy [60], IDegLira led to a greater reduction of HbA1c (−0.44%) and body weight (−1.42 Kg) compared with iGlarLixi, at similar insulin doses. However, there are no head-to-head trials comparing short- and long-acting GLP-1RAs in addition to insulin therapy in type 2 diabetes.

The most frequent schedule of combination therapy generally consists of a basal insulin associated with a short-acting GLP-1RA or the once daily-administered liraglutide, as separate preparations of each component (free or flexible combo) or as a fixed ratio combo. There is evidence from a recent meta-analysis of 11 RCTs that the two combo strategies (free- and fixed-ratio combo) lead to similar results in terms of HbA1c decrease, body weight reduction, and risk of hypoglycaemia, when compared with up-titration of basal insulin therapy [61].

Other emerging therapeutic schedules include the use of a once-weekly GLP-1RA added to a single injection of a long-acting insulin analog [39–41,45] or to multiple injections of a short-acting insulin analog before meals [47,51]. The addition of long-acting GLP-1 RAs could be particularly useful when fasting glucose target is not achieved with basal insulin, and improvements of both fasting and post-prandial glucose are required. In this context, the use of a GLP-1RAs administered once weekly offers the advantage of avoiding additional daily injections other than basal insulin. On the other hand, the addition of a once weekly GLP-1RA to meal-time insulin represents an effective treatment option for type 2 diabetic patients who need intensification of therapy, without increasing the number of daily injections [47,51].

Main strengths of our work are related to the comprehensive systematic search that included all the RCTs published until March 2019, the double-checking of data extraction, the conduction of pre-planned sub-group analyses, and the inclusion of a significant number of studies of high quality (18 out 36).

Some limitations need also to be acknowledged. The high degree of between-study heterogeneity and the evidence of publication bias for three outcomes (proportion of patients at target, risk of hypoglycemia, and weight change) may limit the generalizability of the results. Using the GRADE approach, we assessed the certainty of the evidence to be moderate or low for the outcomes of interest, mainly based on the inconsistency of the results, reducing the strength of inference we can make from the results. The reasons for the high heterogeneity may be related to the intrinsic characteristics of the included studies, namely clinical features of participants in the studies, the different comparator therapies included, the GLP-1RA preparations used, the background therapy, and the trials' design. Moreover, most studies were sponsored by industry (31 out 36), had too short duration to assess long-

term effects of the combo, and used an open-label design (22 out 36).

Combination therapy of GLP-1RA and insulin could represent a valuable treatment strategy to improve metabolic control in the management of type 2 diabetes. This combination presents a higher efficacy associated with a slight increase of hypoglycemia and weight loss when compared with other injectable therapy (insulin up-titration or GLP-1RA alone), and similar efficacy when compared with insulin regimens (basal-plus or basal-bolus), with low risk of hypoglycemic events and more weight loss. Further studies with longer follow-up are needed to assess the durability, tolerability, and progression to diabetes complications.

Authors' contribution

M. I. M., D. G., and K.E. contributed to the study design. M.I.M. and D.G. conducted the literature search, data extraction, and data analysis and wrote the manuscript. P. C. and D. G. did the statistical analyses. G. B., L.S., and M.L. contributed to the data analysis and to writing the manuscript. K. E. and D. G. reviewed and edited the manuscript. All authors have approved the final article.

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Declaration of Competing Interest

D.G. reports honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, NovoNordisk. K. E. reports honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, Boehringer Ingelheim, NovoNordisk. M.I.M. reports honoraria for speaking at meetings from Astrazeneca, NovoNordisk, Sanofi-Aventis, and a consultancy fee from MSD. G.B. reports honoraria for speaking at meetings from Novartis.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.06.009.

REFERENCES

[1] American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S90–S102. 10.2337/dc19-S009.

[2] Riddle MC, Rosenstock J, Gerich J. Insulin Glargine 4002 study investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–6. https://doi.org/10.2337/diacare.26.11.3080.

[3] Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51:408–16. https://doi.org/10.1007/s00125-007-0911-x.

[4] Dale J, Martin S, Gadsby R. Insulin initiation in primary care for patients with type 2 diabetes: 3-year follow-up study. Prim Care Diabetes 2010;4:85–9. https://doi.org/10.1016/j.pcd.2010.03.001.

[5] Curtis B, Lage MJ. Glycemic control among patients with type 2 diabetes who initiate basal insulin: a retrospective cohort study. J Med Econ 2014;17:21–31. https://doi.org/10.3111/13696998.2013.862538.

[6] Reid T, Gao L, Gill J, Stuhr A, Traylor L, Vlajnic A, et al. How much is too much? Outcomes in patients using high-dose insulin glargine. Int J Clin Pract. 2016;70:56–65. https://doi.org/10.1111/ijcp.12747.

[7] Giorgino F, Bonadonna RC, Gentile S, Vettor R, Pozzilli P. Treatment intensification in patients with inadequate glycemic control on basal insulin: rationale and clinical evidence for the use of short-acting and other glucagon-like peptide-1 receptor agonists. Diabetes Metab Res Rev 2016;32:497–511. https://doi.org/10.1002/dmrr.2775.

[8] Cimmaruta D, Maiorino MI, Scavone C, Sportiello L, Rossi F, Giugliano D, et al. Efficacy and safety of insulin-GLP-1 receptor agonists combination in type 2 diabetes mellitus: a systematic review. Expert Opin Drug Saf 2016;15(sup2):77–83. https://doi.org/10.1080/14740338.2016.1221402.

[9] 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;384:2228–34. https://doi.org/10.1016/S0140-6736(14)61335-0.

[10] 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;40:614–24. https://doi.org/10.2337/dc16-1957.

[11] Singhal M, Unni S, Schauerhamer M, Nguyen H, Hurd J, McAdam-Marx C. Real-world glycemic control from GLP-1RA therapy with and without concurrent insulin in patients with type 2 diabetes. J Manag Care Spec Pharm 2017;23(267–275). https://doi.org/10.18553/jmcp.2017.16334.

[12] Montvida O, Klein K, Kumar S, Khunti K, Paul SK. Addition of or switch to insulin therapy in people treated with glucagon-like peptide-1 receptor agonists: A real-world study in 66 583 patients. Diabetes Obes Metab 2017;19:108–17. https://doi.org/10.1111/dom.12790.

[13] Price H, Blüher M, Prager R, Phan TM, Thorsted BL, Schultes B. EXTRA study group. Use and effectiveness of a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) in a real-world population with type 2 diabetes: Results from a European, multicentre, retrospective chart review study. Diabetes Obes Metab 2018;20:954–62. https://doi.org/10.1111/dom.13182.

[14] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, 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;62:e1–e34. https://doi.org/10.1016/j.jclinepi.2009.06.006.

[15] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 Available from www.handbook.cochrane.org.. The Cochrane Collaboration 2011.

[16] Ryan R, Hill S. How to GRADE the quality of the evidence. Cochrane consumers and communication group; 2016,

available at http://cccrg.cochrane.org/author-resources. Version 3.0 December 2016.
[17] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[18] Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[19] Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2011;154:103–12. https://doi.org/10.7326/0003-4819-154-2-201101180-00300.
[20] DeVries JH, Bain SC, Rodbard HW, Seufert J, D'Alessio D, Thomsen AB, et al. Liraglutide-Detemir Study Group. 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;35:1446–54. https://doi.org/10.2337/dc11-1928.
[21] Li CJ, Li J, Zhang QM, Lv L, Chen R, Lv CF, 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;11:142. https://doi.org/10.1186/1475-2840-11-142.
[22] Seino Y, Min KW, Niemoeller E, Takami A. EFC10887 GETGOAL-L Asia study investigators. 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;14:910–7. https://doi.org/10.1111/j.1463-1326.2012.01618.x.
[23] 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;36:2489–96. https://doi.org/10.2337/dc12-2454.
[24] 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;36:2497–503. https://doi.org/10.2337/dc12-2462.
[25] Buse JB, Vilsbøll T, Thurman J, Blevins TC, Langbakke IH, Bøttcher SG, et al. Trial investigators. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care 2014;37:2926–33. https://doi.org/10.2337/dc14-0785.
[26] de Wit HM, Vervoort GM, Jansen HJ, de Grauw WJ, 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;57:1812–9. https://doi.org/10.1007/s00125-014-3302-0.
[27] Gough SC, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, et al. NN9068-3697 (DUAL-I) trial investigators. 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;2:885–93. https://doi.org/10.1016/S2213-8587(14)70174-3.
[28] 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;16:827–32. https://doi.org/10.1111/dom.12286.
[29] Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, de Loredo L, Tornøe K, et al. NN2211-3917 Study Group. 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;17:1056–64. https://doi.org/10.1111/dom.12539.
[30] 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) h5364. BMJ 2015;351. https://doi.org/10.1136/bmj.h5364.
[31] 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;18:663–70. https://doi.org/10.1111/dom.12661.
[32] Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G, et al. LixiLan-L trial investigators. 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. Diabetes Care 2016;39:1972–80. https://doi.org/10.2337/dc16-1495.
[33] Lingvay I, Pérez Manghi F, García-Hernández P, Norwood P, Lehmann L, Tarp-Johansen MJ, et al. DUAL V investigators. 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 2016;315:898–907. https://doi.org/10.1001/jama.2016.1252.
[34] Rosenstock J, Diamant M, Aroda VR, Silvestre L, Souhami E, Zhou T, et al. LixiLan PoC study group. Efficacy and safety of LixiLan, 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;39:1579–86. https://doi.org/10.2337/dc16-0046.
[35] Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. LixiLan-O trial investigators. 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. Diabetes Care 2016:2026–35. https://doi.org/10.2337/dc16-0917.
[36] 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;7:565–73. https://doi.org/10.1111/jdi.12457.
[37] 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;176:939–47. https://doi.org/10.1001/jamainternmed.2016.1540.
[38] 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;8:101–14. https://doi.org/10.1007/s13300-016-0218-3.

[39] 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;19:1024–31. https://doi.org/10.1111/dom.12937.
[40] Guja C, Frías JP, Somogyi A, Jabbour S, Wang H, Hardy E. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. Diabetes Obes Metab 2018;20:1602–14. https://doi.org/10.1111/dom.13266.
[41] 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;103:2291–301. https://doi.org/10.1210/jc.2018-00070.
[42] Yang W, Min K, Zhou Z, Li L, Xu X, 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;20:335–43. https://doi.org/10.1111/dom.13072.
[43] Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, et al. 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37:2763–73. https://doi.org/10.2337/dc14-0876.
[44] Mathieu C, Rodbard HW, Cariou B, Handelsman Y, Philis-Tsimikas A, Ocampo Francisco AM, et al. VICTOZA ADD-ON (NN1250-3948) study group.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;16:636–44. https://doi.org/10.1111/dom.12262.
[45] Rosenstock J, Fonseca VA, Gross JL, Ratner RE, Ahrén B, Chow FC, et al. Harmony 6 Study Group. 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;37:2317–25. https://doi.org/10.2337/dc14-0001.
[46] 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;30:521–9. https://doi.org/10.1002/dmrr.2561.
[47] 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;385:2057–66. https://doi.org/10.1016/S0140-6736(15)60936-9.
[48] FLAT-SUGAR trial investigators. 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;39:973-81. 10.2337/dc15-2782.
[49] Rosenstock J, Guerci B, Hanefeld M, Gentile S, Aronson R, Tinahones FJ, et al. GetGoal duo-2 trial investigators. 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;39:1318–28. https://doi.org/10.2337/dc16-0014.
[50] 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;19:1669–80. https://doi.org/10.1111/dom.12985.
[51] 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;6:605–17. https://doi.org/10.1016/S2213-8587(18)30104-9.
[52] 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;41:1009–16. https://doi.org/10.2337/dc17-1114.
[53] 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;9:119–26. https://doi.org/10.1111/jdi.12654.
[54] 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. https://doi.org/10.1016/j.diabres.2018.03.032.
[55] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2018;2018(41):2669–701. https://doi.org/10.2337/dci18-0033.
[56] 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;51:417–28. https://doi.org/10.1007/s12020-015-0718-3.
[57] Maiorino MI, Bellastella G, Esposito K, Giugliano D. Premixed insulin regimens in type 2 diabetes: pros. Endocrine 2017;55:45–50. https://doi.org/10.1007/s12020-016-0917-6.
[58] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. NDA 208583 approval letter. November 21, 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208583Orig1s000TOC.cfm Accessed June 17, 2018; U.S. Food and Drug Administration, Center for Drug Evaluation and Research. NDA 208583 approval letter. November 21, 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208673Orig1_toc.cfm Accessed June 17, 2018.
[59] Andersen A, Lund A, Knop FK, Vilsbøll T. Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol 2018;14:390–403. https://doi.org/10.1038/s41574-018-0016-2.
[60] Evans M, Billings LK, Håkan-Bloch J, Slothuus U, Abrahamsen TJ, Andersen A, et al. An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (IDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin. J Med Econ 2018;21:340–7. https://doi.org/10.1080/13696998.2017.1409228.
[61] 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;20:2309–13. https://doi.org/10.1111/dom.13343.