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Key Messages

- No direct comparison between fixed ratio combinations (FRC) of basal insulins and GLP-1 receptor agonists (IDegLira and iGlarLixi) is available.
- Based on a network meta-analysis of randomized trials, no difference between FRCs were found in HbA1c and the risk of hypoglycaemia, while weight gain was lower with IDegLira compared to iGlarLixi.
- Our findings may help in individualizing the selection of the best FRC for a given patient.

Keywords: GLP-1 agonists, lixisenatide, liraglutide, basal insulins, insulin glargine, insulin degludec, network meta-analysis

Word count:

Key messages:	371 (≤420)
Abstract:	250 (≤250)
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Abstract

Aims: To compare the efficacy and safety of commercially available fixed ratio combinations (FRC) of glucagon-like peptide 1 receptor agonists (GLP-1RA) and basal insulins by a network meta-analysis (NMA) of randomised controlled trials (RCT) of type 2 diabetes patients.

Methods: We report a systematic review and network meta-analyses of RCTs of type 2 diabetes patients randomized to FRCs or to their components for ≥24-weeks reported in PubMed or ClinicalTrials.gov until 28/FEB/2022. Primary outcome was attained HbA1c. Secondary outcomes included fasting plasma glucose, change in body weight, and incident hypoglycaemia. Treatment effects were estimated as mean differences and standard errors (MD; [SE]) or odds ratios (OR) with 95% confidence intervals (95%CI) using iGlarLixi as reference.

Results: We included 29 RCTs of the 1404 papers identified. No direct comparison between FRCs were found. After excluding some insulin capped trials to reach model consistency, both FRCs were more efficacious regarding HbA1c than their components, however no difference between FRCs were found (MD: -0.10 [SE: 0.10]%). The effect of IDegLira (-0.47 [0.24] mmol/l) and basal insulins was similar to that of iGlarLixi (ref.) on fasting glucose, while GLP-1RA had lower efficacy than iGlarLixi. Weight gain was lower with GLP-1RAs and IDegLira (-0.72 [0.32] kg) than iGlarLixi (ref.) and higher with basal insulins. Incident hypoglycemia (based on different definitions) was least frequent with GLP-1RAs followed by IDegLira (OR 0.78 95%CI 0.39-1.57), iGlarLixi (ref.) and basal insulins.

Conclusions: Regarding HbA1c, both FRCs were more efficacious over their individual components with similar efficacies of the two FRCs.

Introduction

As type 2 diabetes is a progressive disease, treatment intensification becomes necessary in many patients.[1, 2] Insulin remains the ultimate glucose-lowering therapy and it is recommended when patients cannot achieve glycaemic targets with lifestyle changes and non-insulin antidiabetic agents.[2, 3]

Basal insulin therapy improves fasting plasma glucose (FPG) at the expense of an increased risk of nocturnal hypoglycaemia and some weight gain,[4] whereas glucagon-like peptide 1 receptor agonists (GLP-1RAs) have a marked effect on postprandial plasma glucose (PPG) and produce weight loss.[5, 6] When combined with basal insulin, GLP-1RAs do not increase the risk of hypoglycaemia and can mitigate weight gain associated with insulin therapy.[7-13] While both agents are highly efficacious, these effects are limited to an HbA1c decrease of 0.5-1.5% for GLP-1 RAs and increasing risk of hypoglycaemia with higher basal insulin doses.[5-13]

The combination of these agents offer an efficacious option with an acceptable side effect profile demonstrated in several randomized trials [9-16]and thus their co-application is supported by treatment guidelines.[17]

Currently two commercially available prefilled fixed ratio combination (FRC) of basal insulin and GLP-1 RA are available in clinical practice that had proven better efficacy than either of their components.[9-13, 18] The first, the combination of insulin degludec and liraglutide (IDegLira) was tested in the DUAL clinical trial program.[9, 10, 18] The other, a combination of insulin glargine and lixisenatide (iGlarLixi) was tested in the LixiLan clinical trial program.[11-13]

Given their simple titration and once daily administration, these FRCs are emerging as feasible alternatives to basal-bolus therapy.[7, 19] However, the comparative efficacy of these FRCs is equivocal. Two meta-analyses reached differing conclusions. One suggesting similar efficacy the other

superiority of IDegLira.[20, 21] The methodology (including trial selection and data synthesis) of these meta-analyses raises further questions.[22]

Thus, we aimed to compare the efficacy and safety of the available 2 fixed ratio combinations (IDegLira and iGlarLixi) using all available randomized evidence by performing a formal network meta-analysis.

Methods

Setting

We report a systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analyses) extension statement for network meta-analyses.[23]

Data Sources and Searches

We searched PubMed and ClinicalTrials.gov from inception to 28/FEB/2022 without language or date restrictions using the terms [‘glargine’, ‘degludec’, ‘lixisenatide’, ‘liraglutide’, ‘IDegLira’, ‘iGlarLixi’]. Then titles were checked for randomized controlled trials. See details in **Supplementary Table 1**

Study Selection

We included randomized controlled trials of at least 24-week duration that compared at least any two of the following eligible interventions: insulin glargine 100 IU/ml, insulin degludec, lixisenatide, liraglutide, iGlarLixi, IDegLira. See details in **Supplementary Table 2**. After deduplication, each report was assessed for eligibility at the abstract level and for those potentially eligible, full texts were retrieved and examined by two reviewers. Conflicts were resolved by consensus under the supervision of a senior researcher (AGT).

Data Extraction

Data extraction was performed by two reviewers and discrepancies were resolved by consensus under the supervision of a senior researcher (AGT). We used a predesigned data collection form to extract study characteristics, baseline characteristics of participants, and efficacy and safety outcomes. The primary outcome was the HbA1c level achieved (mean and standard deviation [SD]) for each treatment arm at the last observation. Secondary outcomes included achieved fasting plasma glucose (mean and SD), change in body weight from randomization (mean and SD), number of participants experiencing at least one hypoglycaemic event (measured and/or symptomatic using the definition utilized in the given study). For hypoglycaemic events, we also extracted its definition for each study.

Risk-of-Bias Assessment

Risk of bias for each study was assessed separately for each outcome by 2 reviewers using the Cochrane Collaboration recommendations.[24] Discrepancies were resolved by consensus under the supervision of a senior researcher (AGT).

Risk of bias was evaluated based on the following characteristics: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Risk of bias was considered to be low, when all domains were deemed to have low risk and high when at least 1 domain had high risk or at least 3 domains were deemed to have some concerns. The remaining studies were categorized as some concerns about bias.

Evaluation of the Confidence in Quality of the Evidence provided by the Network Meta-Analysis

We used the CINeMA (Confidence in Network Meta-analysis) Internet tool (https://cinema.ispm.unibe.ch/) to determine the confidence in the quality of the network estimates.

The CINeMA tool investigates within study bias according to the usual GRADE guidelines described in the previous point. Publication bias was investigated using funnel plots and Begg's tests for comparisons with at least 4 trials (degludec vs. glargine U100, iGlarLixi vs. glargine U 100), for all other comparisons we entered some concern. For the evaluation of imprecision, heterogeneity, and

incoherence (aka inconsistency), we used clinically significant differences (0.4% for HbA1c, 0.5 mmol/l for fasting blood glucose, 1.5 kg for weight change, and 0.7 for the odds ratio of any hypoglycaemia).[25, 26] For the overall rating, we kept the grade if only 1 measure had some concern, decreased the confidence by 1 grade if 2 measures had some concerns, by 2 grades if more than two measure had some concern, and by 3 grades if a major concern was present.[27]

Data Synthesis and Analysis

We performed frequentist random-effects network meta-analyses using mvmeta command and routines in Stata.[28] Treatment effects were estimated as mean differences (MD) and standard errors [SE] for continuous outcomes and odds ratios (OR) for dichotomous outcomes with 95% confidence intervals (Cl) with iGlarLixi as the reference treatment.

First, we created network plots for each outcome where the node size is proportional to the number of participants assigned to a given treatment arm and the thickness of lines between nodes corresponds to the number of studies assessing a given comparison.[29]

Then, we investigated the extent of inconsistency in the networks by fitting an inconsistency model. If the overall χ^2-test for inconsistency was non-significant, we report the estimates from the consistency model. We also tested for heterogeneity within the network by comparing the direct and indirect estimates using the sidesplit and forest commands. Visual inspection suggested that the inconsistency was related to comparisons where the FRCs were compared to basal insulins and basal insulin doses were capped. We ranked the studies based on the standardized difference between the insulin cap and the mean insulin dose used in the insulin arm. After sequential removal of the studies from the smallest to the largest standardized difference to reach a consistency model, only 2 studies [11, 13] remained of those with an insulin cap. (**Supplementary Table 3**)

Next, treatments were ranked and reported graphically as cumulative probability lines with respective standard errors for each treatment. We also provide the rescaled mean ranks (SUCRA). SUCRA is 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst.[30]

We also ran two sets of sensitivity analyses. First, only the LixiLan-L and LixiLan-O trials were kept from the studies with an insulin cap in the analysis of fasting blood glucose, weight change and incident hypoglycaemia. Second, we repeated the analysis after the exclusion of all studies that included participants on basal insulin at baseline.

All analyses were conducted using Stata/IC, v15 (StataCorp, TX, USA).

Results

Overview of Trials

The study selection process in shown in **Supplementary Figure 1.** Our searches yielded a total of 1404 records. First, we excluded all studies that were not randomized controlled trials (RCT). This resulted in 232 remaining records. Then we excluded studies on type 1 diabetes, repeat publications, studies shorter than 24 weeks duration, studies that reported only on glargine 300 IU/ml, meta-analyses of RCTs, and studies with an inadequate control group. Finally, we included 29 RCTs into our network meta-analysis.

As the network plots for each outcome are very similar, for the sake of simplicity, we only show the case for fasting glucose. For the HbA1c analysis, we only included the LixiLan-L and LixiLan-O trials to be able to reach model consistency.[11, 13] For the fasting glucose analysis, we excluded the EAGLE trial (comparing liraglutide with glargine) as no laboratory measured fasting glucose was reported in the paper.[31] For the weight change and the hypoglycaemia analysis, we excluded the I'D GOT and the Devote trials due to missing data (both comparing degludec and glargine insulins).[32, 33] (**Figure 1)**

The network plot clearly shows that patients were allocated to 6 interventions: IDegLira, insulin degludec, insulin glargine 100 IU/ml, iGlarLixi, lixisenatide, and liraglutide. Most patients were randomized to the basal insulins and much lower numbers were randomized to GLP-1RAs or FRCs. Consequently most direct evidence was on the comparison between basal insulins. No direct comparison between the FRCs was found and while glargine was compared to both FRCs, none of the other components (i.e. basal insulin or GLP-1 RA) of one manufacturer was compared to the FRC of the other manufacturer. (**Figure 1**)

The most important baseline characteristics of included studies are presented in **Table 1**. We included 29 studies with altogether 23,605 participants. There were 11 studies (#1-11) that compared degludec to glargine insulin. All randomized patients were on oral antihyperglycemic drugs (OAD) however 8 studies allowed the use of basal insulins before entry. There is only one direct comparison between the GLP-1RAs (#12) where patients received OADs before study entry. Patients treated with only OADs before study entry were compared to both GLP-1RAs and basal insulins, while those on insulin before entry were only compared to basal insulins.

Study durations varied between 24 and 104 weeks. The mean age of patients varied between 55-65 years, and the mean diabetes duration between 6 and 14 years. In those studies where insulin was used before entry, duration of diabetes was somewhat longer. The mean HbA1c was around 8% in most studies at baseline, however there were 4 outliers (# 9, #17, #22, #27) where the mean HbA1c was above 8.5%. The average BMI was at or above 30 kg/m^2 except for the Asian investigations, in which it was lower at 25-30 kg/m^2**.** (**Table 1**)

All studies had moderate or low risk of bias. Most studies were open label leading to some concern that is related to differences in the titration protocols of the compared products. (**Table 1, Supplementary Table 4-7**)

HbA1c level at study end

After exclusions, the consistency model fitted the network. Using iGlarLixi as the reference treatment, the estimated effect sizes and their standard errors are presented in **Table 2.**

We found a negative point estimate in the comparison of IDegLira and iGlarLixi, however the observed difference was neither clinically nor statistically significant (-1.10 SE -1.09 mmol/mol; -0.10 SE 0.10%). All other drugs were less efficacious compared to iGlarLixi (all p<0.05). (**Table 2**)

The ranking of the different treatments clearly shows the superiority of the FRCs over their components as IDegLira and iGlarLixi have a 100% cumulative probability being the best treatments with the highest probability (SUCRA 1.0 and 0.8, respectively). Gla-100 (SUCRA 0.5) and liraglutide (SUCRA 0.5) rankings followed by degludec (SUCRA 0.2) and lixisenatide (SUCRA 0.0) that has an almost 100% probability of being the worst medication of these. (**Figure 2A**)

Fasting glucose at study end

There was no significant difference between the FRCs in terms of the final fasting glucose according to the consistency model, however the point estimate favoured IDegLira and degludec by 0.2-0.5 mmol/l. Glargine had similar efficacy to iGlarLixi, while GLP-1 agonists were less efficacious. (**Table 2**)

The ranking shows that medications that contain degludec (IDegLira SUCRA 1.0, degludec SUCRA 0.8) have the highest probability being the most efficacious followed by iGlarLixi (SUCRA 0.6) and glargine (SUCRA 0.4). GLP-1 RAs have the worst ranking with liraglutide (SUCRA 0.2) having a better rank than lixisenatide (SUCRA 0.0). (**Figure 2B**)

Change in body weight from randomization to end of study

There was an approximately 0.72 kg difference (p<0.05) in weight gain between the FRCs favouring IDegLira. GLP-1RAs were associated with a 2.1 to 3.4 kg smaller weight increase, while basal insulins with an over 1 kg larger weight increase compared to iGlarLixi (all p<0.05). (**Table 2**)

The ranking also shows that there are 3 groups of medications with GLP-1 RAs being the first 2 (SUCRA 1.0 and 0.8), FRCs the third and fourth (SUCRA 0.4 and 0.6) and basal insulins the worst in terms of weight gain (SUCRA 0.1 both). (**Figure 2C**)

Incident hypoglycaemia

The risk of any hypoglycaemia was non-significantly lower by 22% with IDegLira compared to iGlarLixi. However the lowest risk was found with GLP-1 RAs (79 to 81% less than with iGlarLixi). The risk of hypoglycaemia was similar with basal insulins and iGlarLixi. (**Table 2**)

The ranking of compounds shows a similar picture to the consistency model estimates with GLP-1RAs having the lowest risk (SUCRA 0.9), followed by IDegLira (SUCRA 0.5), glargine (SUCRA 0.3), then degludec and iGlarLixi (SUCRA 0.2 both). (**Figure 2D)**

Confidence in Quality of the Evidence

Our confidence in the evidence based on the direct and indirect comparisons using the CINeMA tool is reported in the **Supplementary Material**. Regarding the comparison of the two FRCs our confidence is moderate for HbA1c, weight change, and the risk of hypoglycaemia, while it is low for fasting glucose. (**Supplementary Tables 4-7**)

Sensitivity analysis

Our sensitivity analyses mainly confirmed the results for all outcomes of the main analyses regarding the comparison between the FRCs. (Data available on request.)

Discussion

We report the results of a network-meta-analysis (NMA) comparing the efficacy and safety of two fixed-ratio combinations of a GLP-1RA and a basal insulin (IDegLira and iGlarLixi). As to the best of our knowledge, no direct comparisons of these drugs are available, thus an NMA of randomized trials

gives the highest level of evidence regarding this comparison. Our results showed no statistically significant difference in terms of HbA1c, fasting glucose, and the risk of hypoglycaemia. Furthermore based on the confidence intervals, the difference in HbA1c is unlikely to be clinically relevant. In terms of fasting glucose, the point estimate (0.47 mmol/l), is relatively large but imprecise. Similarly a clinically significant effect on the risk of hypoglycaemia cannot be excluded especially in people prone to hypoglycaemia. In contrast, we found statistically significant differences in terms of weight change that favoured IDegLira over iGlarLixi. However, the clinical relevance of the weight difference (~0.7 kg) is questionable.

The efficacy of the 2 commercially available fix combinations has been evaluated in two prior meta-analyses that have methodological limitations. The first from Cai et al. is an indirect meta-analysis including 8 studies that reported no significant difference in HbA1c or FPG changes from baseline between the investigated FRCs. This methodology has at least 3 potential problems. First, the authors expect the placebo effect to be of similar magnitude in all studies. Second, the effect of the FRCs thought to be similar irrespective of the background medications. These assumptions however are untenable as evidenced by the high I^2 values of the meta-analyses. Third, by using the changes from baseline, all information on the comparator arm is omitted, and randomized trials are treated as observational studies.[21] Furthermore, as a letter to the editor commented, the used indirect meta-analysis is an outworn method for this comparison as an NMA would give a more precise result using all available evidence.[22]

The other attempt by Evans et al. included only 4 studies, those that compared FRCs to basal insulins in people who already received basal insulin before the study. They found that the treatment with IDegLira resulted in a greater reduction of HbA1c, higher odds of reaching HbA1c<7%, and a greater reduction in body weight, compared with iGlarLixi.[20] Both analyses shown in the paper is based on the assumption that the effect of the insulin cap on the outcomes are the same in the Dual-II and in the LixiLan-L trials. However, the lower insulin cap (50 vs 60 IU) and a lower target blood glucose (4.4-5.6 mmol/l vs. 4-5 mmol/l) in DUAL-II compared to LixiLan-L led to a lower proportion of

participants that reached the insulin dose they would have used without an insulin cap (15-20 v 75-80%) and thus this assumption seems not to hold.[11, 14, 20] (**Supplementary Table 3**)

The importance of these methodological limitations and potential bias in the estimates of the investigations further highlighted by the fact that these estimates may be introduced into cost effectiveness models. Indeed there are 3 papers comparing the cost-effectiveness (cost-utility) of the commercially available FRCs.[34-36] Given the fact that 2 of these papers that found IDegLira to be cost saving were based on the results of Evans et al. and the third (based on observational data) found iGlarLixi cost saving, our estimates based on a more sophisticated method could provide less biased input for the cost-effectiveness analysis.[20, 34-36]

Individual RCTs and their meta-analyses has found that FRCs are more efficacious compared to their components.[9, 18, 37-39] This notion seems also to be true for the free combinations of GLP-1 RAs and basal insulins, however FRCs have the advantage of a simpler treatment regimen.[16] These findings are in line with our observation on the ranking of treatments included in the present NMA. We found that FRCs were equally efficacious, that lixisenatide had the smallest effect on HbA1c, while basal insulins and liraglutide had similar efficacies. Furthermore, according to some limited evidence, FRCs could have similar or even better efficacy compared to basal-bolus insulin therapy.[7, 40, 41]

There is no direct comparison between the FRCs and the results of the two previous meta-analyses are probably unreliable due to their methodological drawbacks.[20, 21] We found no statistically significant difference in the efficacy of these two compounds and the relatively narrow confidence intervals argue against clinical significance.

However, to reach a consistency model, we had to exclude some trials. While these studies are statistical outliers, their exclusion also seems to be substantiated clinically based on the bias introduced by the cap of insulin doses. As it can be appreciated in **Supplementary Table 3**, trials that

utilized an insulin cap are quite different regarding the proportion of participants that reached the insulin dose they would have reached without the cap. It is very likely that the insulin arm of the DUAL-II trial could not reach its HbA1c potential, while the effect of the insulin cap in LixiLan-L and LixiLan-O is probably negligible. In the rest of the trials with the insulin cap, less than two third of the participants reached the insulin dose that would have been used without the cap. While the difference in the insulin cap between DUAL-II and the LixiLan trials seems to be relatively small (10 IU), the target blood glucose range was higher (4.4-5.6 mmol/l vs. 4-5 mmol/l) in the latter trials driving to even lower basal insulin doses.[9, 11, 12]

Regarding the FPG lowering effect, we found that FRCs and basal insulins had no statistically significant differences in their efficacies. However the FPG level reached with IDegLira and degludec were numerically lower than those with iGlarLixi and glargine. This observation is not surprising and its clinical relevance is questionable given that according to meta-analyses comparing degludec and glargine, lower FPGs were reached without any difference in HbA1c.[42, 43] Our result are also consistent with the previous indirect meta-analysis of Cai et al.[21] Both GLP-1 receptor agonists fared worst in their FPG lowering effect.

The previous RCTs, their meta-analyses and our results clearly showed that the effect of FRCs on body weight falls between their components: their use is associated with less weight gain compared to insulins and more than GLP-1RAs alone.[9, 11, 13, 16, 38] The limited meta-analyses of Evans et al. also found that FRCs were associated with less weight gain compared to basal insulins.[20, 21]
Our findings refine the above notions: (1) both basal insulins have almost the same effect on body weight, (2) weight gain is around 1 kg less with compounds containing liraglutide compared to those containing lixisenatide.

In general, hypoglycaemia was more frequent with basal insulins and FRCs in efficacy trials compared to GLP-1RAs.[16, 38] Furthermore, hypoglycaemia was less frequent with FRCs compared to basal plus and basal-bolus insulin regimes.[7] Individual RCTs found no difference in the risk of

hypoglycaemia between iGlarLixi and glargine or IDegLira and degludec in the DUAL I trial, while the risk was lower with IDegLira compared to degludec in the DUAL II and V trials. Our results mostly confirm these observations showing the lowest risk of hypoglycaemia (based on the rankograms) with liraglutide and lixisenatide, then substantially higher with IDegLira, iGlarLixi, and basal insulins. Our findings are inconclusive regarding the difference between FRCs: a non-significant, 22% lower point estimate for hypoglycaemia with IDegLira compared to iGlarLixi. Given the wide confidence intervals, a clinically significant difference between the FRCs cannot be excluded. While the risk of hypoglycaemia is similar with iGlarLixi and basal insulins, the efficacy of iGlarLixi is better (by around 0.5-0.6%) compared to basal insulins. It should be noted that 60-70% of participants in the included RCTs had no hypoglycaemic events during the 24-30 weeks of follow-up suggesting that the potential hypoglycaemia advantage of IDegLira is relevant only to people with an increased risk of hypoglycaemia.[9, 11, 13, 39]

Furthermore, the included RCTs used different definitions of hypoglycaemia meaning that our results on this outcome are only hypothesis generating. The cut-off for measured hypoglycaemia in most studies comparing IDegLira to other compounds was blood glucose<3.1 mmol/l, in the rest of the studies it was blood glucose<3.9 mmol/l. The lower cut-off may have increased the power to show differences between compounds.[44] It should be noted that the clinical relevance of ‘mild’ hypoglycaemia (3.1-3.9 mmol/l) is undeniable.[45]

The main strength of our study is the use of a formal network meta-analysis for the comparison of 2 compounds that have not been directly compared in randomized controlled trials. This methodology uses the totality of evidence with comparisons of the investigated FRCs or their components. In contrast, previous attempts to compare these medications were selective in their use of the published trials.[20, 22]

Furthermore, the rankings provide information on the specific benefits of the unique medications that can be considered in a given clinical situation in line with the ADA/EASD consensus guideline.[3]

Our study has some limitations that has to be acknowledged. Any meta-analysis is only as good as the studies included. We had to exclude some of the trials in the HbA1c analysis due to statistical considerations, however this exclusion was also logical, based on available data on trial design. The included trials used different definitions of hypoglycaemia that may have biased our results on this outcome. It should be noted however that these definitions were consistent within studies, and some evidence suggests that relative risks remain mostly constant over different hypoglycaemia definitions.[44] In addition, most of the included studies were open label thus at some risk of bias. However, because of the different titration schedules of the different medications, double blinding may not be the optimal design in these particular comparisons.[46] Moreover, the included studies have a relatively short duration and thus are unable to provide information on long-term outcomes.

Our results seem to be in conflict with the observation of Huthmacher et al. who reported a significantly larger effect of long acting GLP-1RAs on HbA1c and fasting glucose compared to short acting GLP-1RAs on top of basal insulin treatment. Although one reason for this difference may be related to the limited statistical power of our analysis, we think that the special titration schedule of FRCs compared to free combinations is a more likely explanation. While in the studies of free combinations either basal insulin or GLP-1 receptor agonists are titrated to a maximal dose, the dosing of fixed ratio combinations (unless the maximal dose is reached) would provide submaximal doses of both components. Furthermore, iGlarLixi has 2 different insulin – GLP-1 receptor agonist ratio combinations that makes comparisons of free and fixed combinations problematic.[47]

Furthermore, our network meta-analysis leaves a clinically very important question unanswered regarding the potential superiority of free combinations of GLP-1RAs and basal insulins over the FRCs. With the availability of oral or once weekly GLP-1RAs, these treatments could provide more flexibility with similar amount of complexity and inconvenience as the FRCs.[3]

Conclusion

Our study shows similar efficacy of IDegLira and iGlarLixi, which were clearly superior over their individual components for glycaemic control. In persons with marked hyperglycaemia, FRCs provide more robust glucose-lowering over daily GLP-1RAs or basal insulins, though treatment decisions may need to consider hypoglycaemia mitigation and desire for weight loss as additional considerations where GLP-1RAs alone may be suitable.

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Author contribution statement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Study design and conception: GAV and AGT. Analysis and interpretation: all authors. Drafting of the article: GAV and AGT. Critical revision for intellectual content: all authors. AGT had full access to all the data used in these analyses and takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and accepted the submitted version of this manuscript.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. General characteristics of included studies and baseline characteristics of participants

ID	Suppl. Reference number	Trial name	Registration #	Publ. year	n	Follow-up (weeks)	Arm 1	Arm 2	Arm 3	Pre-study treatment	Age (years)	female	Duration (years)	BMI (kg/m2)	HbA1c(mmol/mol / %)	Fasting BG (mmol/l)
1	1	**Begin basal-bolus**	nct00972283	2012	1006	52	deg	gla-100		insulin+-OADs	58,9 SD 9,3	46%	13,5 SD 7,2	32,1 SD 4,6	68.3 SD 9.8 / 8.4 SD 0.9	9,2 SD 3,1
2	2	**Begin once long**	nct00765817	2012	1030	52	deg	gla-100		OADs	59,1 SD 9,8	38%	9 SD 6,6	31,25 SD 4,6	66.1 SD 8.7 / 8.2 SD 0.8	9,65 SD 2,6
3	3	**Begin easy am**	nct01068678	2013	459	26	deg	gla-100		OADs	58,4 SD 9,9	43%	8,85 SD 6,06	32,45 SD 5,25	67.2 SD 9.3 / 8.3 SD 0.9	9,45 SD 2,4
4	3	**Begin easy pm**	nct01076647	2013	467	26	deg	gla-100		OADs	57,3 SD 9,6	43%	8,8 SD 4,4	32,1 SD 5,3	67.2 SD 8.7 / 8.3 SD 0.8	9,9 SD 2,3
5	4	**Begin Flex**	nct01006291	2013	455	26	deg	gla-100		OADs	56,4 SD 9,6	50%	10,8 SD 6,65	29,65 SD 4,5	69.4 SD 9.8 / 8.5 SD 0.9	8,9 SD 2,8
6	5	**Begin Low Volume**	nct01068665	2013	460	26	deg	gla-100		OADs	57,5 SD 9,2	47%	8,2 SD 6,17	32,45 SD 5,53	67.2 SD 10.4 / 8.3 SD 1	9,65 SD 2,75
7	6	**Begin Once Asia**	nct01059799	2012	435	26	deg	gla-100		OADs	58,6 SD 9,9	46%	11,45 SD 6,5	25,2 SD 3,55	69.4 SD 8.7 / 8.5 SD 0.8	9,65 SD 2
8	7	**Pan et al.**	nct01849289	2016	833	26	deg	gla-100		OADs	55,9 SD 9,7	50%	7,95 SD 5,4	27,2 SD 4,65	67.2 SD 9.3 / 8.3 SD 0.9	9,4 SD 2,45
9	8	**I'D GOT**	umin000011827	2017	44	24	deg	gla-100		OADs	64,2 SD 14,2	55%	10,8 SD 11,2	24,66 SD 4,29	73.8 SD 16.1 / 8.9 SD 1.5	6,8 SD 1,73
10	9	**Devote**	nct01959529	2017	7637	104	deg	gla-100		OADs or inj.	65 SD 7,4	37%	16,4 SD 8,85	33,6 SD 6,8	68.3 SD 18 / 8.4 SD 1.7	9,5 SD 3,9
11	10	**Switch 2**	nct02030600	2017	720	32	deg	gla-100		basal insulin+- OADs	61,6 SD 10,4	47%	7,5 SD 1,1	32,3 SD 5,7	58.5 SD 12 / 7.5 SD 1.1	7,5 SD 2,8
12	11	**Lira vs. Lixi**	nct01973231	2016	404	26	lira	lixi		metformin	56,2 SD 10,3	41%	6,4 SD 5,1	34,7 SD 6,7	68.3 SD 8.7 / 8.4 SD 0.8	10,4 SD 2,3
13	12	**LixiLan-L**	nct02058160	2016	738	30	iGlarLixi	gla-100		basal insulin+OADs	59,6 SD 9,05	53%	12,05 SD 6,75	31,15 SD 4,25	69.4 SD 7.7 / 8.5 SD 0.7	7,95 SD 1,8
14	13	**Lixilan-O**	nct02058147	2016	1170	30	iGlarLixi	gla-100	lixi	OADs	58,4 SD 9,3	49%	8,8 SD 5,7	31,7 SD 4,4	68.3 SD 7.7 / 8.4 SD 0.7	9,8 SD 2,3
15	14	**Lixilan-POC**	nct01476475	2016	323	24	iGlarLixi	gla-100		metformin	56,7 SD 9,45	18%	6,7 SD 4,82	32,1 SD 4,6	66.1 SD 8.7 / 8.2 SD 0.8	9,72 SD 2,2
16	15	**Dual-I**	nct01336023	2014	1663	26	IDegLira	deg	lira	OADs	55 SD 9,9	49%	6,8 SD 5,4	31,2 SD 5,1	67.2 SD 8.7 / 8.3 SD 0.8	9,2 SD 2,5
17	16	**Dual-II**	nct01392573	2014	398	26	IDegLira	deg		basal insulin+met+- OADs	57,5 SD 10,04	46%	10,5 SD 6,5	33,7 SD 6	72.7 SD 7.7 / 8.8 SD 0.7	9,65 SD 3
18	17	**Dual-V**	nct01952145	2016	557	26	IDegLira	gla-100		insulin+met	58,8 SD 9,6	50%	11,4 SD 7	31,7 SD 4,45	67.2 SD 9.8 / 8.3 SD 0.9	8,9 SD 2,7
19	18	**LixiLan JP-O1**	nct02749890	2020	321	26	iGlarLixi	lixi		OADs	58 SD 10,7	58%	8.67 SD 6.21	26.82 SD 4.3	68.3 SD 6.6 / 8.4 SD 0.6	9.725 SD 1.66
20	19	**LixiLan JP-O2**	nct02752828	2020	521	26	iGlarLixi	gla-100		OADs	59,7 SD 10,65	35%	9,25 SD 6,62	25,5 SD 4,32	66.1 SD 5.5 / 8.2 SD 0.5	8,64 SD 0,92
21	20	**LixiLan JP-L**	nct02752412	2020	512	26	iGlarLixi	gla-100		basal insulin+OAD(s)	59,8 SD 10,45	40%	11,94 SD 7,39	25,1 SD 4	66.1 SD 5.5 / 8.2 SD 0.5	7,73 SD 1,39
22	21	**EAGLE**	nct01117350	2015	978	24	lira	gla-100		OADs	57,2 SD 8,8	46%	8,5 SD 24,6	31,9 SD 4,1	66.6 SD 10.9 / 9 SD 1	NA SD NA
23	22	**Pasquel et al**	nct01919489	2021	273	26	lira	gla-100		OADs	56 SD 10,4	40%	9,65 SD 8,5	33,4 SD 5,3	67.8 SD 9.8 / 8.4 SD 0.9	NA SD NA
24	23	**LEAD-5**	nct00331851	2009	581	26	lira	gla-100		OADs	57,5 SD 9,93	40%	9,44 SD 6,13	30,54 SD 5,24	66.8 SD 9.8 / 8.3 SD 0.9	9,16 SD 2,04
25	24	**Guo et al**	ChiCTR2000035091	2020	96	26	lira	gla-100		metformin	52,6 SD 6,59	41%	NA SD NA	28,71 SD 3,91	68.6 SD 11.8 / 7.4 SD 1.1	7,26 SD 1,38

26	25	**Yan et al**	nct02147925	2019	75	26	lira	gla-100		metformin	44,8 SD 8,89	31%	NA SD NA	29,8 SD 3,2	60.7 SD 11.9 / 7.7 SD 1.1	8,62 SD 2,51
27	26	**Watada et al**	nct02911948	2019	210	26	IDegLira	deg		basal insulin+OAD(s	56 SD 10,2	37%	14,05 SD 7,61	27,7 SD 3,8	70.3 SD 9.2 / 8.6 SD 0.8	8,79 SD 2,56
28	27	**Kaku et al**	nct02607306	2019	819	52	IDegLira	deg	lira	OADs	57,2 SD 10,07	29%	9,43 SD 6,04	26,4 SD 4,36	68.6 SD 11.7 / 8.4 SD 1.1	9,87 SD 2,3
29	28	**DUAL-IX**	nct02773368	2019	420	26	IDegLira	gla-100		OADs	56,7 SD 10,3	41%	9,5 SD 6,25	31,2 SD 4,8	67.2 SD 12 / 8.3 SD 1.1	9,55 SD 2,55

Arm – treatment arm

deg – insulin degludec

gla-100 – insulin glargine 100 IU/ml

lira – liraglutide

lixi – lixisenatide

IDegLira – fixed combination of insulin degludec and liraglutide

iGlarLixi – fixed combination of insulin glargine 100 IU/ml and lixisenatide

OAD – oral antihyperglycemic drug

inj. – injectional antidiabetic treatment

met – metformin

BG – blood glucose

Table 2. Estimated effect sizes and 95% confidence intervals with iGlarLixi as the reference for each outcome based on consistency models

	HbA1c (mmol/mol)	HbA1c (%)	Fasting glucose (mmol/l)	Weight change (kg)	Incident hypoglycaemia (OR)
iGlarLixi	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	1 (ref.)
IDegLira	-1.1 (-3.2; 1)	-0.10 (-0.30; 0.10)	-0.47 (-0.94; 0.00)	-0.72 (-1.35; -0.09)*	0.78 (0.39; 1.57)
Glargin U100	4.3 (2.8; 5.8)*	0.39 (0.25; 0.53)*	0.15 (-0.18; 0.49)	1.29 (0.85; 1.73)*	0.92 (0.56; 1.52)
Degludec	5.1 (3.4; 6.9)*	0.47 (0.31; 0.63)*	-0.21 (-0.60; 0.18)	1.28 (0.75; 1.82)*	0.99 (0.55; 1.81)
Lixisenatide	10.2 (8.2; 12.1)*	0.93 (0.75; 1.11)*	1.91 (1.44; 2.40)*	-2.10 (-2.76; -1.45)*	0.21 (0.09; 0.48)*
Liraglutide	3.8 (1.9; 5.8)*	0.35 (0.17; 0.53)*	0.56 (0.08; 1.03)*	-3.35 (-3.99; -2.72)*	0.19 (0.09; 0.38)*

* Significant at $p<0.05$.

IDegLira – fixed combination of insulin degludec and liraglutide

iGlarLixi – fixed combination of insulin glargine 100 IU/ml and lixisenatide

OR – odds ratio

Figure legends

Figure 1 Network plots of treatment comparisons including all 29 studies (outcome: fasting glucose)

Each node corresponds to a drug, and the node size is proportional to the number of participants assigned to that drug. Each line represents a direct comparison between drugs, and the width of the line is proportional to the number of randomized controlled trials providing data for the comparison.

Deg – insulin degludec

Gla-100 – insulin glargine 100 IU/ml

Lira – liraglutide

Lixi – lixisenatide

IDegLira – fixed combination of insulin degludec and liraglutide

iGlarLixi – fixed combination of insulin glargine 100 IU/ml and lixisenatide

Figure 2 The cumulative rank diagram of the investigated treatments for HbA1c (A), fasting blood glucose (B), weight change (C), and incident hypoglycaemia (D)

For example, **Panel A** shows that only the FRCs have any chance of being the best treatments over their components. Both FRCs have a 100% cumulative probability of being the best or second best treatments Either liraglutide or Gla-100 have any chance of being the 3rd ranking medications. Degludec has a very low chance of being the 4th in the rankings but has a 100% cumulative probability to be the 5th ranking medication. Finally, lixisenatide has the last place in the ranking.

Deg – insulin degludec

Gla-100 – insulin glargine 100 IU/ml

Lira – liraglutide

Lixi – lixisenatide

IDegLira – fixed combination of insulin degludec and liraglutide

iGlarLixi – fixed combination of insulin glargine 100 IU/ml and lixisenatide