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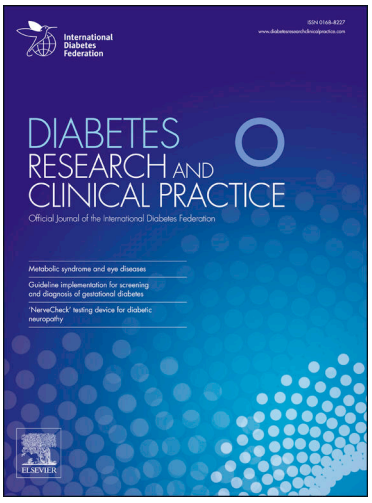

Review

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Review

Titratable fixed-ratio combination of insulin glargine plus lixisenatide: A simplified approach to glycemic control in type 2 diabetes mellitus

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ABSTRACT

Approximately 50% of patients with type 2 diabetes mellitus (T2DM) do not achieve glycemic targets and require treatment intensification. A fixed-ratio combination of a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with basal insulin, such as lixisenatide with insulin glargine (iGlarLixi), exploits the complementary mechanisms of action of each component to address hyperglycemia while mitigating potential adverse events (AEs). The iGlarLixi dose is titrated considering the effect of basal insulin on fasting plasma glucose, and the fixed-ratio combination ensures that the lixisenatide dose never exceeds 20 µg/day. We describe the characteristics of iGlarLixi therapy, based on the LixiLan clinical program, and provide guidance on the characteristics of patients likely to benefit from such treatment in routine clinical practice. In the phase III LixiLan trials, iGlarLixi resulted in significantly greater reductions in glycated hemoglobin (HbA1c), better achievement of HbA1c targets, less glycemic variability versus insulin glargine, lixisenatide or GLP-1 RA alone, and was associated with weight control, less hypoglycemia versus insulin glargine, and fewer GI AEs versus lixisenatide. Findings were consistent regardless of age, diabetes duration, and baseline HbA1c. The efficacy, safety, and convenient once-daily administration schedule of iGlarLixi make it a valuable treatment option for patients with T2DM requiring treatment intensification.

Keywords:

Fixed-ratio combination

Insulin glargine

Lixisenatide

Type 2 diabetes

Hypoglycemia

Bodyweight

1. Introduction

The substantial increase in the prevalence of type 2 diabetes mellitus (T2DM) poses growing challenges for the long-term management of the disease. In patients with T2DM, early intervention to accomplish and retain glycemic control is essential to lower the risk of diabetes-related long-term complications [1]. However, several studies have shown that between 40% and 60% of patients worldwide are not achieving their glycemic goals [2-6], increasing the risk of such complications. Current treatment guidelines recommend that patients achieve and maintain a personalized target of glycated hemoglobin (HbA1c), often below 7%, with the option to adjust this target depending on certain clinical characteristics, such as age, life expectancy, presence of complications or comorbidities, and compliance to therapy. Moreover, the target might vary between different countries or regions due to different local clinical recommendations and guidelines [7]. The timely identification of patients failing to achieve their appropriate HbA1c target is important to ensure that treatment can be modified promptly. Estimates suggest that 24% to 54% of patients with T2DM around the world have ‘residual hyperglycemia’, defined as HbA1c not at target in the presence of relatively well-controlled fasting glucose. This is often seen in patients on basal insulin (BI) failing to meet their target HbA1c and who may benefit from the addition of a prandial therapy. Residual hyperglycemia is, therefore, an important unmet clinical need, and its presence should prompt physicians to initiate treatments than can result in improved postprandial glycemic control [8,9].

The pathophysiological complexity of T2DM is such that disease progression is often inevitable, even in patients who adhere to treatment and show an adequate response in terms of glycemic control. However, adherence to antihyperglycemic medication varies widely and is often inadequate, seldom reaching the 80% threshold for "good" adherence [10]. Poorer adherence in patients with T2DM in the real-world occurs regardless of the particular treatment regimen, and with both oral and injectable formulations. Regimen complexity, dosing frequency, and potential adverse events (AEs), such as weight gain or hypoglycemia, have all been shown to be barriers to adherence, which is essential to achieve glycemic control [10].

The development of progressive beta-cell dysfunction with defects in endogenous insulin response is associated with an uninterrupted deterioration of glycemic control, even during optimal therapy with oral anti-diabetes drugs (OADs) and glucagon-like peptide-1 receptor agonist (GLP-1 RA); this often leads to consideration of insulin therapy, usually consisting in the initiation of BI.

Although therapeutic inertia can be evident at each step of the treatment algorithm, resistance to intensification appears to be more pronounced when initiating or implementing BI therapy. Furthermore, few patients intensify their insulin regimen in a timely and appropriate manner [7,11]. Alternative therapies should be offered in the case of poor response to GLP-1 RA [12] or if patients do not achieve their HbA1c target within one year of starting BI, as real-world data show that the likelihood of achieving glycemic control remains low if it is not achieved within 12 months [13]. The selection of the appropriate treatment should be based upon multiple parameters related to the clinical characteristics of the patient as well as to

the features of the drugs, such as mechanism of action, potency in controlling hyperglycemia, capability of achieving clinically significant outcomes, potential impact on non-target organs such as the heart, kidney, and liver, potential adverse effects (hypoglycemia, gastrointestinal [GI] AEs, others), body weight gain, ease of use, likelihood of patient's adherence, and cost [14].

Antihyperglycemic therapy in patients with T2DM not meeting their HbA1c target on BI can be intensified by adding a GLP-1 RA or initiating multiple daily insulin injections using a basal-plus or basal-bolus (BP/BB) insulin regimen [7]. These two treatment approaches were evaluated in a systematic review and meta-analysis, showing that, in patients with uncontrolled T2DM, treatment intensification with GLP-1 RA/insulin combinations provided similar antihyperglycemic efficacy as a BP/BB regimen, with the additional advantages of weight loss, fewer hypoglycemic episodes and use of a lower insulin dose [15]. Fixed-ratio combinations of BI and GLP-1 RA are a new therapeutic option for patients with T2DM who are not controlled on BI therapy; however, pre-emptive guidance is required to guarantee suitable and safe switching to these therapies to ensure glucose control in people with T2DM [16].

2. Purpose and literature review

iGlarLixi is a titratable fixed-ratio combination of insulin glargine (iGlar) and lixisenatide (Lixi) that is administered once daily. In clinical studies, iGlarLixi had better efficacy than either iGlar or Lixi alone and was associated with less weight gain than iGlar alone and fewer GI AEs than Lixi alone, without increasing the risk of

hypoglycemia. iGlarLixi may, therefore, offer a new option for therapy intensification in patients with uncontrolled T2DM [17].

The purpose of this review is to describe the characteristics of iGlarLixi therapy, focusing on its safety, efficacy, and feasibility, and to provide guidance on the characteristics of patients likely to benefit from such treatment in routine clinical practice.

The Authors conducted a comprehensive search of the peer-reviewed literature listed in the PubMed database, using combinations of the terms “iGlarLixi”, “type 2 diabetes”, “clinical trial”, “review”, “real world”, “efficacy”, “safety”. The initial search took place on July 2, 2019 and was subsequently updated as the manuscript was developed. All English-language studies assessing the efficacy and/or safety of iGlarLixi were selected for evaluation. Articles of interest were identified initially based on the title and abstract, with a final selection made once the full-text copy had been obtained and reviewed. Additional relevant publications were identified from the bibliographies of the full-text articles obtained through the initial PubMed search, and by screening abstracts from recent prominent diabetes conferences.

Also, the Authors performed a subgroup analysis (Review Manager version 4.5.0) to assess the impact of baseline HbA1c and BMI, duration of T2DM and age on the mean change in HbA1c and body weight and on the incidence of hypoglycemia in the iGlarLixi group vs. the iGlar group across the LixiLan program.

3. Rationale for fixed-ratio combinations

The combination of BI with a GLP-1 RA is promising because the complementary mechanisms of the individual treatments may enhance the therapeutic benefit while also limiting the potential for AEs associated with their exclusive use (Figure 1). BI therapy improves fasting plasma glucose (FPG) and nocturnal hyperglycemia, whereas GLP-1 RAs, especially the short-acting molecules, significantly impact postprandial glucose (PPG) and prandial glucose excursions. In combination with BI, GLP-1 RAs do not increase the risks of hypoglycemia and can counteract the weight gain associated with insulin therapy. The once-daily, prandial GLP-1 RA Lixi (Lyxumia; Sanofi, Paris, France) lowers PPG largely by delaying gastric emptying and decreasing prandial glucagon levels. The complementary effects of Lixi plus BI given as separate injections were shown in the GetGoal clinical trials, including the GetGoal Duo-2 trial, which evaluated patients with T2DM with inadequate glycemic control on BI, with or without oral therapy with 1-3 OADs. In GetGoal Duo-2, adding Lixi to iGlar (100 U/mL), with or without metformin, led to similar improvements in glycemic control and was associated with less hypoglycemia and weight gain compared with a BP/BB insulin regimen [18].

While treatment should be individualized according to the clinical characteristics of the patient and the properties of the medications, multiple barriers to optimal treatment exist, for both patients and providers. Patient concerns may also include the convenience of treatments, impact on their daily lives, and potential social stigma. Practical barriers related to medication cost or access may also affect treatment decisions [19]. Due to the multifaceted pathophysiology of T2DM, patients often require a combination of different therapies to meet glycemic targets, and fixed-

ratio combinations permit multiple drugs to be administered as simple regimens [20]. Furthermore, adding a short-acting GLP-1 RA to BI may be more convenient than adding meal-time injections of rapid-acting insulin, eliminating the need for patients to modify meal portions and carbohydrate levels, and reducing issues of insulin omission or non-adherence [19]. Lixi and iGlar have comparable physicochemical characteristics, so a defined fixed ratio of the two components can be mixed in a single product (iGlarLixi or LixiLan) that is administered as a once-daily injection, thus reducing the number of injections [18]. These advantages are likely to be appreciated by patients and may help them to adhere to treatment [21]. Not surprisingly, therefore, physicians have reported better treatment satisfaction among patients receiving a fixed-dose combination compared with combination therapy using separate agents [22]. Fixed-dose combinations of GLP-1 RA and BI have shown clinical efficacy in hyperglycemia correction, as well as weight control and sparing of hypoglycemic events, and this has impacted on the most recent clinical recommendations [23]. The spectrum of potential benefits associated with the use of iGlarLixi indicates that it may be considered as an interesting option to intensify BI therapy [24].

4. iGlarLixi

iGlarLixi contains a fixed ratio of iGlar and Lixi in a 3-mL prefilled injection pen for subcutaneous administration. The efficacy of Lixi over a wide dose range, alone or in combination with iGlar in the iGlarLixi fixed-ratio combination, has been evaluated in a few studies and summarized in a recent review by Frias and colleagues [25]. Although maximal reduction of PPG area under the curve required more than

12.5 µg of Lixi, a relevant effect was already detectable at a dose as low as 5 µg of Lixi (44% of the reduction achievable with the maximal dose of 20 µg of Lixi). This set of studies demonstrates that the dose range of Lixi (5–20 µg) in the iGlarLixi combination is clinically effective over a wide range to achieve adequate control of PPG levels.

There are two dose levels available in Europe; both contain 100 U/mL of iGlar, but the Lixi dose is 50 µg/mL in the '10:40 Pen' and 33 µg/mL in the '30:60 Pen' [26]. In the US, the approved dose is 100 U/mL of iGlar and 33 µg/mL of Lixi [27]. In Japan, the approved dose is 100 U/mL of iGlar and 100 µg/mL of Lixi [28]. When compared with BI, the insulin/GLP-1 RA fixed-ratio combination of iGlarLixi is superior in reducing HbA1c, without any increase in hypoglycemia risk, and with some weight loss rather than gain [18,29]. Overall, iGlarLixi therapy is perceived as simple and with a low incidence of AEs, thus potentially increasing patients' adherence [30]. iGlarLixi was approved by the US Food and Drug Administration (FDA) in 2016 and the European Medicines Agency (EMA) in 2017 to improve glycemic control in adults with T2DM [26,27]. In Europe, iGlarLixi is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycemic control as an adjunct to diet and exercise in addition to metformin with or without sodium-glucose cotransporter-2 (SGLT-2) inhibitors [26], whereas the US indication is not limited by prior medications [27].

4.1. Initiation and titration of iGlarLixi

The two commercially available pens of iGlarLixi containing a different combination of iGlar and Lixi (100/50 in the '10:40 Pen' [2 units iGlar U100: 1 mcg Lixi] and 100/33 in the '30:60 Pen' [3 units iGlar U100: 1 mcg Lixi]). The '10:40' and '30:60' pens allow an insulin dose range of 10–40 or 30–60 units, respectively. The iGlar dose can be adjusted between 10 and 60 units/day with the two pens (Europe), and between 15 and 60 units/day with the 100/33 pen (US), but the Lixi dose is always limited to a maximum of 20 µg/day, irrespective of which pen the patient is using [18,20,26,27]. The dose of iGlarLixi needs to be titrated based on the required dose of iGlar to control the patient's FPG [27,30]. A dose titration algorithm to increase the dose by 2 units if the FPG is between 100-140 mg/dL (5.6 and 7.8 mmol/L) or by 4 units if >140 mg/dL (7.8 mmol/L) is often followed [29]. Because iGlarLixi is a fixed-ratio combination, the Lixi dose is thus gradually increased following BI titration. The known GI AEs of Lixi are minimized by the slow incremental dose increase; moreover, the Lixi doses attained using iGlarLixi are usually lower than those achieved when Lixi is administered alone (usually 3-7 µg less), contributing to the reduction in GI AEs.

4.2. Main results from randomized controlled trials (LixiLan-O, LixiLan-L, LixiLan-G)

Randomized controlled clinical studies were carried out to assess the efficacy and safety of iGlarLixi [31].

The LixiLan-O trial (n = 1170) compared iGlarLixi with iGlar or Lixi in patients with T2DM who had inadequate glycemic control during treatment with metformin alone

or in combination with a second OAD. The primary study outcome was the change in HbA1c at 30 weeks. The mean age in the overall patient population was 58.4 years, with a mean T2DM duration of 8.8 years, and a mean body mass index (BMI) of 31.7 kg/m^2. Mean HbA1c at baseline was 8.1% (65 mmol/mol) and decreased by 1.6% in patients taking iGlarLixi, compared with reductions of 1.3% in patients taking iGlar ($P < 0.0001$ vs. iGlarLixi) and 0.9% in patients taking Lixi ($P < 0.0001$ vs. iGlarLixi) (Figure 2a). The final HbA1c was 6.5% (48 mmol/mol) in the iGlarLixi group, 6.8% (51 mmol/mol) in the iGlar group, and 7.3% (56 mmol/mol) in the Lixi group. More patients in the iGlarLixi group (74%) achieved target HbA1c <7% compared with the iGlar group (59%) or Lixi group (33%) ($P < 0.0001$ for all). Mean body weight decreased by 0.3 kg in patients receiving iGlarLixi and by 2.3 kg in patients receiving Lixi, while it increased by 1.1 kg in those receiving iGlar ($P < 0.0001$), with a significant weight difference of 1.4 kg between the iGlarLixi and iGlar groups ($P < 0.0001$) (Figure 2d) [18].

The LixiLan-L trial compared the efficacy and safety of iGlarLixi with those of iGlar in patients with T2DM (n = 736) inadequately controlled on BI, with or without treatment with up to two OADs. Patients receiving iGlarLixi showed a significantly greater reduction in HbA1c from baseline compared with those receiving iGlar (–1.1% vs. –0.6%, $P < 0.0001$) (Figure 2a), such that the mean HbA1c at 30 weeks was 6.9% (52 mmol/mol) in the iGlarLixi group and 7.5% (58 mmol/mol) in the iGlar group. More individuals achieved a target HbA1c <7% with iGlarLixi (55%) versus iGlar (30%). The twin benefit of glycemic control (HbA1c <7%) without weight gain was noted in 34% of iGlarLixi patients compared with 13% of iGlar patients [29].

Mean body weight decreased by 0.7 kg in patients receiving iGlarLixi and increased by 0.7 kg in those receiving iGlar (between-group difference of 1.4 kg, P < 0.0001) (Figure 2d) [29].

In the LixiLan-G study, switching to iGlarLixi improved glucose control for patients with T2DM insufficiently controlled on a maximum tolerated dose of a GLP-1 RA plus oral antihyperglycemic agents. LixiLan-G was a randomized, 26-week, open-label trial that compared switching to iGlarLixi with continuing prior GLP-1 RA therapy in 514 patients inadequately controlled by GLP-1 RA plus oral antihyperglycemic therapy [12]. Patients receiving iGlarLixi showed a significantly greater reduction from baseline in HbA1c compared with those receiving continuing on GLP-1 RA (–1.0% vs. –0.4%, P < 0.0001) (Figure 2a), such that the mean HbA1c at 26 weeks was 6.7% (50 mmol/mol) in the iGlarLixi group and 7.4% (57 mmol/mol) in the GLP-1 RA group. More individuals achieved a target HbA1c <7% with iGlarLixi versus continued GLP-1 RA (62% and 26%, respectively; P < 0.0001). Interestingly, treatment with iGlarLixi significantly improved not only fasting but also prandial glycemic control (Figure 2b,c). Also, as expected, body weight increased in the iGlarLixi group while it decreased in the GLP-1RA group (Figure 2d). Results from the single-arm, 26-week extension period for LixiLan-G showed that the efficacy and tolerability of iGlarLixi were maintained up to Week 52 [12].

4.3. Post-hoc analyses

To evaluate the effect of various patients characteristics in LixiLan-O, efficacy and safety were compared in subgroups of patients with different baseline HbA1c

(<8% or ≥8% [<64 or ≥64 mmol/mol]), T2DM duration (<7 or ≥7 years) or BMI (<30 or ≥30 kg/m^2). In all subgroups, iGlarLixi was significantly more effective than either iGlar or Lixi monotherapy in decreasing HbA1c from baseline to Week 30 [32].

Similarly, in the LixiLan-L trial, the benefits of iGlarLixi over iGlar were independent of baseline HbA1c or BMI ($P < 0.0001$ for all comparisons) [33]. While mean HbA1c reductions at Week 30 were consistently greater in the iGlarLixi group than the iGlar group in all subgroups with different baseline HbA1c levels, patients with higher baseline HbA1c tended to achieve greater reductions with either treatment. In a separate analysis, for patients with baseline HbA1c ≤8%, ≤9%, and >9%, the mean reductions in the iGlarLixi group were –1.1%, –1.4%, and –2.4%, respectively, compared with –0.5%, –1.0%, and –1.8% in the group receiving iGlar (all $P < 0.0001$ for iGlarLixi vs. iGlar). In each HbA1c subgroup, a higher proportion of patients receiving iGlarLixi achieved an HbA1c <7% compared with the group receiving iGlar (74.2%, 54.7%, and 52.2% with iGlarLixi vs. 37.2%, 31.6%, and 23.5% with iGlar, respectively). In all subgroups, there was no increase in the risk of hypoglycemia with iGlarLixi compared with iGlar [34]. Moreover, in LixiLan-L, iGlarLixi was more efficacious than iGlar in reducing HbA1c regardless of disease duration, thus also in patients with longstanding T2DM (i.e., with diabetes duration >15.7 years) who are often poorly responsive to therapies; particularly in these patients, iGlarLixi showed a lower incidence of hypoglycemia than iGlar, indicating that the fixed-ratio combination may mitigate the increased risk of hypoglycemia often seen in longstanding T2DM [35]. Similarly, an exploratory analysis of the LixiLan-G trial showed that treatment with iGlarLixi remained beneficial regardless of

diabetes duration and C-peptide levels [36]. These results show that the effect of iGlarLixi is largely independent of beta-cell function, as previously also shown for Lixi [37]. This is particularly important given that patients with reduced beta-cell function were previously only considered for insulin therapy [13,33].

A *post-hoc* analysis of LixiLan-O and LixiLan-L revealed that iGlarLixi was significantly more effective than iGlar or Lixi in reducing HbA1c at Week 30 in older patients (≥65 years). This age-based analysis found that iGlarLixi effectively reduced the extent of weight gain associated with insulin and GI AEs associated with Lixi, with similar results in patients aged ≥65 and <65 years [38].

The test for subgroup differences indicated that baseline HbA1c and BMI, T2DM duration and age did not modify the effect of iGlarLixi compared to iGlar on change in HbA1c (p=0.97, Figure 3), body weight (p=0.61, Figure 4) and incidence of hypoglycemia (p=0.75, Figure 5).

Another *post-hoc* analysis examined outcomes in patients from the LixiLan-L and LixiLan-O trials stratified by their baseline risk. Patients (n = 1181) were categorized as either low-risk (LR; healthier patients who had been assigned an HbA1c goal of <7%), or high-risk (HR) patients (n = 717) (aged >65 years or with comorbidities, and with an HbA1c goal of <8%). In LixiLan-L, iGlarLixi reduced HbA1c more effectively than iGlar in both LR and HR patients (change from baseline, –1.1% vs. −0.6% for iGlarLixi vs. iGlar in both LR and HR groups; P < 0.001). Similarly, in LixiLan-O, the change from baseline in HbA1c at Week 30 was −1.6% for iGlarLixi versus −1.3% for iGlar and −0.8% for Lixi in LR patients (P < 0.01) and −1.4% versus −1.2% and

−0.9%, respectively (P < 0.01) in HR patients (P < 0.01). The reduction in PPG levels was also significantly greater with iGlarLixi than with comparators in both the LR and HR subgroups (P < 0.001). The incidence of hypoglycemia was similar among risk categories in all treatment groups [39].

Further *post-hoc* analysis of the two studies examined the time to glycemic control and found that 60% and 46% of the patients treated with iGlarLixi achieved target HbA1c of <7% at 12 weeks, compared to only 45% and 24% of the patients treated with iGlar. The median time to target HbA1c was 85.0 days with iGlarLixi versus 166.0 days with iGlar in LixiLan-O (P < 0.0001), and 153 days with iGlarLixi and never reached with iGlar in LixiLan-L (P < 0.001). The time to target FPG was similar in the iGlarLixi and iGlar groups, as was the incidence of hypoglycemic events. Thus, in patients with T2DM not adequately controlled on OADs or BI, iGlarLixi resulted in more patients achieving glycemic control early on in treatment compared with iGlar [40].

4.4. Propensity score matching of patients for sequential vs. simultaneous treatment with Lixi and iGlar

Propensity-score matching is a validated statistical approach for indirectly comparing therapeutic outcomes that allows better comparison of different patient populations by minimizing confounding factors [41]. The effect of simultaneous administration of the fixed-ratio combination of iGlarLixi was compared with the sequential combination of iGlar plus Lixi using the data from the LixiLan and the GetGoal Duo programs and propensity-score matching to account for baseline

clinical and biochemical covariates [18,24,29,42,43]. The data suggest that using the iGlarLixi combination rather than the sequential addition of Lixi to initiate or intensify BI treatment may be more effective for blood glucose control, as shown by lower HbA1c achieved; in addition, such an approach is able to provide better weight control and is associated with fewer GI AEs [43].

A potential marker of PPG control during BI therapy is the difference between bedtime and morning glucose levels. Relevant to this concept, a *post-hoc* analysis of the LixiLan-L study in patients inadequately controlled on BI showed that patients receiving iGlarLixi had significantly greater reductions in the bedtime-to-morning glucose differential, compared with patients receiving iGlar [44]. Fewer fluctuations between morning and night-time glucose levels suggest superior control of both fasting and prandial glucose, and closer match between treatment and physiologic needs.

Often, patients with T2DM experience “residual hyperglycemia” (e.g., HbA1c ≥7.0% despite FPG <140 mg/dL). In a recent post hoc analysis of the LixiLan-L study, the proportion of patients with residual hyperglycemia was similar in both treatment arms at screening, but after 30 weeks declined more with iGlarLixi than with iGlar (23.8% with iGlarLixi vs. 47.1% with iGlar). Moreover, the proportion of patients achieving both HbA1c (<7.0 %) and FPG (<140 mg/dL) targets was about 2-fold greater with iGlarLixi compared iGlar. These results indicate that iGlarLixi is effective in reducing residual hyperglycemia in patients with T2DM on BI therapy [45].

HbA1c is used as a measure of glycemic control because it reflects the mean glucose concentration over time and, therefore, the ongoing burden of glycemia. However, it does not accurately reflect day-to-day glycemic variability (GV). Data from the LixiLan-O and the LixiLan-L trials found that, by Week 30, iGlarLixi improved a range of GV parameters from baseline, with no increase in the risk of hypoglycemia. Patients receiving iGlarLixi showed significant improvements in self-measured plasma glucose (SMPG), mean absolute glucose, mean amplitude of glycemic excursions, high blood glucose index (HBGI), and area under the SMPG curve for each patient (AUCn), compared with patients receiving iGlar, as well as significant improvements in SMPG, HBGI, and AUCn compared with patients receiving Lixi [46].

4.5. Propensity score matching of patients comparing LixiLan-L and BB in Get-Goal Duo-2

Compared with BB insulin, iGlarLixi was associated with improved glucose control, weight loss, and fewer hypoglycemic events [27,47]; in the propensity score matched analysis of the LixiLan-L and Get-Goal Duo-2 studies, the treatment differences for HbA1c reduction was - 0.28% (P = 0.0002), for weight change was -1.32 kg (P < 0.0001), and for the rate of hypoglycemic events per patient-year was 2.85 (P < 0.0001), all in favor of iGlarLixi [47].

4.6. Comparison between iGlarLixi and iDegLira

iDegLira is another fixed-ratio combination of a GLP-1 RA and a BI with a prolonged action profile, combining 100 U/mL insulin degludec and 3.6 mg/mL

liraglutide; one unit contains one unit of insulin degludec and 0.036 mg of liraglutide. IDegLira is dosed at the same time each day, with or without food [48]. As with iGlarLixi, the clinical utility of iDegLira was established through a clinical development program of phase III efficacy and safety trials [20]. There is evidence that liraglutide may provide added cardiovascular benefit in patients with established cardiovascular disease, whereas evidence for a cardiovascular benefit with lixisenatide has not yet been demonstrated in these patients [49].

In the absence of head-to-head studies, a systematic review and meta-analysis of eight trials indirectly compared iGlarLixi and iDegLira [50]. Compared to baseline, the mean change in HbA1c was -1.50% ($P < 0.01$) after iGlarLixi treatment and -1.89% ($P < 0.01$) after iDegLira treatment; there was no significant between-group difference. Mean body weight decreased by 0.62 kg in the iGlarLixi group ($P \leq 0.01$) and 0.81 kg in the iDegLira group ($P = 0.52$) with no significant between-group difference.

Evans et al. have restricted the indirect comparison of iGlarLixi and iDegLira to patients with T2DM uncontrolled with BI. In this analysis, iDegLira was associated with a greater reduction in HbA1c and body weight and a lower risk of severe hypoglycemia; however, using the ADA definition of symptomatic hypoglycemia for both studies, no significant difference was observed between treatments [51]. Moreover, other analyses have recently found iDegLira to be cost-effective compared to iGlarLixi in patients with uncontrolled T2DM on BI due to reduced incidence and delayed onset of complications [52,53].

A recent indirect comparison between iGlarLixi and iDegLira involving the two studies that have compared these therapies with continued use of GLP-1RA (i.e. LixiLan-G and DUAL III, respectively) showed no difference in terms of the proportion of patients reaching HbA1c target at week 26 and body weight reduction, even though iDegLira demonstrated greater HbA1c and FPG reductions from baseline [54].

4.7. Safety of iGlarLixi

Suggested approaches to increasing patient satisfaction and adherence in patients with T2DM include simplifying the treatment regimen (e.g., with fixed-ratio combinations and less frequent administration) and using medications with a low rate of unwanted side effects such as hypoglycemia [55].

In LixiLan-O and LixiLan-L, both iGlarLixi and iGlar groups experienced a similar number of documented symptomatic hypoglycemic events (1.4 vs. 1.2 and 3.03 vs. 4.22 events/patient-year, respectively), regardless of whether the patients were insulin-naïve or continuing BI [18,29]. In LixiLan-G, the incidence of documented symptomatic hypoglycemia was higher in the iGlarLixi group compared to the continued GLP-1RA group (1.54 vs. 0.08 events/patient-year), as expected [12].

Although Lixi can be associated with GI AEs, the rate of GI AEs during the first few weeks of therapy was lower in patients treated with iGlarLixi (9.6% in LixiLan-L and 11.7% in LixiLan-O) than in patients treated with Lixi (27.5% in LixiLan-O). However, after Day 60, GI AEs were reduced, and rates became similar in the iGlarLixi and Lixi groups. In patients receiving iGlarLixi, GI AEs were intermittent,

usually mild or moderate in severity, and mainly developed during the initial titration phase; the median duration of nausea, vomiting and diarrhea with iGlarLixi were 6.0, 2.0 and 2.5 days, respectively, in LixiLan-L, and 5.0, 1.0 and 3.5 days, respectively, in LixiLan-O [56]. Notably, no patients stopped iGlarLixi treatment due to vomiting and very few (1.1%) discontinued due to nausea. The slow dose escalation, as well as the fact that the maximum Lixi dose of 20 µg is almost never reached, probably account for these results. This is a relevant issue given that GI AEs were among the main reasons for discontinuing GLP-1 RAs in a real-world patient survey [21,57].

Furthermore, as Lixi acts by slowing gastric emptying, iGlarLixi may potentially affect the absorption of oral medications, particularly oral contraceptives, some antibiotics, or drugs with a narrow therapeutic index, or in patients with gastroparesis.

No specific cardiovascular outcome trial of iGlarLixi has been conducted. However, dedicated cardiovascular outcome trials of the individual agents determined that both drugs have a neutral influence on cardiovascular endpoints [58,59].

Diabetic dyslipidemia is a major cardiovascular risk factor. Interestingly, in LixiLan-L at Week 30, the median percent changes in triglycerides remained nearly unchanged with iGlarLixi versus a 6.5% increase with iGlar (P = 0.035); similarly, trends towards better total and LDL cholesterol levels were seen with iGlarLixi versus iGlar. However, in those patients who achieved glycemic targets, lipid parameters improved with iGlarLixi but not with iGlar [60].

5. Considerations on using iGlarLixi in daily clinical practice

The available data indicate that iGlarLixi is effective and well-tolerated in patients with T2DM who need further glycemic control, with a safety profile that is comparable to or better than that of its separate components. Due to its simple administration schedule and low incidence of AEs, iGlarLixi may enhance adherence, which in turn will maximize therapeutic outcomes [20,30]. Moreover, by exploiting complementary mechanisms of action, the fixed-ratio combination therapy may target multiple pathogenetic T2DM defects, while reducing the complexity and burden of treatment for the patient [61].

Therefore, an appropriate clinical context for considering the iGlarLixi fixed-ratio combination is that of patients who are unable to achieve adequate control on OADs and are taking neither BI nor a GLP-1 RA. Rather than introducing BI or a GLP-RA first and then adding the other type of agent, patients might be initiated on iGlarLixi as soon as the need for intensification has been identified, especially if they will require robust glucose-lowering; however, this therapeutic option is not reimbursed in some countries. The iGlarLixi fixed-ratio combination therapy is also appropriate for patients who are already taking either a BI or a GLP-1 RA but still show insufficient glycemic control. Specific patients who may particularly benefit from such a therapy include those who want to avoid the multiple injections required with prandial insulin in an insulin intensification regimen, as well as the frequent blood glucose testing needed to adjust prandial doses and lessen the risk of hyper/hypoglycemia. Also, iGlarLixi may be a preferred option for patients concerned about weight gain and hypoglycemia associated with insulin therapy or experiencing

GI AEs with full-dose GLP-1 RA treatment [39,62]. Finally, data from subgroup analysis suggest that this fixed-ratio combination may be effective and well-tolerated regardless of the patient's age and duration of T2DM, BMI, and baseline HbA1c, and to be considered also in older patients with long-standing disease [33]. iGlarLixi is also effective in limiting glucose variability, which is particularly problematic in some patients with T2DM [46].

iGlarLixi is given once daily by subcutaneous injection within 1 hour before the main meal of the day. The dose is titrated according to the patient's insulin requirement considering the fasting glucose target, and the units displayed in the dose window of the iGlarLixi pen represent the glargine dose units. It is critical for both patients and healthcare providers to become well-practiced on how the fixed-ratio combination is prescribed and dosed in order to achieve optimal efficacy and safety [63].

6. Summary and conclusions

The substantial and growing number of people with type T2DM poses a significant challenge for long-term disease management. Furthermore, most patients do not reach or maintain glycemic goals, increasing the risk of a broad range of diabetes-related complications [7,14]. An HbA1c target of <7% is recommended for most adults: if this is not achieved after starting GLP-1 RA, clinical guidelines recommend intensifying treatment with BI or a fixed-dose combination injectable product comprising GLP-1 RA and BI [7,49]. iGlarLixi is a titratable combination of iGlar and Lixi that is administered once daily. Both iGlar and Lixi have been extensively

studied in the treatment of diabetes and have been widely used in clinical practice, and the combination of the two agents provides a rational and effective strategy for use in T2DM, based on their distinct and complementary mechanisms of action. iGlar targets FPG while Lixi targets PPG levels, thus providing a synergistic approach for effective correction of hyperglycemia and attainment of glycemic targets [18,20,27,29].

iGlarLixi was approved by both the FDA and EMA mainly on the basis of two randomized controlled studies, i.e., LixiLan-L and LixiLan-O, and has been further validated through the LixiLan-G study [12,18,29]. In LixiLan-L and LixiLan-O, iGlarLixi has shown superior reductions in HbA1c relative to its individual components, and in LixiLan-G has also proven to be a useful and more effective therapy in patients failing on GLP-1 RA [12]. Furthermore, *post-hoc* analyses, systematic reviews, meta-analyses and real-world studies confirmed the feasibility, efficacy and safety of iGlarLixi in treatment of patients with T2DM [18, 29,31,32,34,35,40,41,43,44,47,56]. The results obtained with iGlarLixi were achieved regardless of diabetes duration, even in patients with T2DM for >15 years, and its benefits are likely to occur independently of the integrity of beta-cell function [33,35].

The most recent American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus guidelines highlight the enhanced glycemic efficacy and lower AEs (specifically GI events and hypoglycemia) with iGlarLixi, while noting that the higher cost of fixed-ratio combinations of BI and GLP-1 RA need to be considered against their "very high" efficacy [49].

The fixed-ratio combination of iGlarLixi allows patients with T2DM to achieve glycemic control in a simple regimen, due to its ease of use and low injection burden for patients. In clinical practice, simplifying the therapeutic approach by using regimens that require fewer injections might translate into better adherence to therapy. This can be further supported by a treatment that, while ameliorating glucose control, does not increase the risk of hypoglycemia and ensures body weight control with a low incidence of AEs. iGlarLixi can thus be considered a useful tool in the therapeutic armamentarium for patients with T2DM requiring additional glycemic control [13,15,20,27,30,39,63].

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Author contributions

FG and RN developed the concept of the manuscript. All authors conducted the literature search and chose the articles for inclusion. All authors reviewed and extensively revised the manuscript during development and approved the final manuscript for submission.

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Figures

Figure 1 – **Insulin and GLP-1 RA in type 2 diabetes mellitus.** FPG: fasting plasma glucose; GLP-1: glucagon-like peptide-1; MoA: mechanism of action; PPG: postprandial glucose; RA: receptor agonist. 1: the combination of basal insulin and long-acting GLP-1 RA. 2: the combination of basal insulin and short-acting GLP-1 RA.

Figure 2 – **Mean changes from baseline in HbA1c (a), fasting plasma glucose (FPG) (b), 2-hours post-prandial glucose (2h-PPG) (c), body weight (d) and incidence of hypoglycemia (≤ 70 mg/dl) (e) across the LixiLan program.** Data are expressed as mean ± SD (a,b,c,d) or percentage (e). *** $p < 0.0001$.

Figure 3 – **Mean change from baseline in HbA1c in the iGlarLixi group vs. the iGlar group stratified by baseline HbA1c, T2DM duration, BMI, and age.** Data were retrieved from subgroup analyses of the LixiLan-L and the LixiLan-O trials. The test for subgroup differences indicated that baseline HbA1c and BMI, T2DM duration and age do not modify the beneficial effect of iGlarLixi compared to iGlar on mean change in HbA1c (p=0.97).

Figure 4 – **Mean change from baseline in body weight in the iGlarLixi group vs. the iGlar group stratified by baseline HbA1c, T2DM duration, BMI, and age.** Data were retrieved from subgroup analyses of the LixiLan-L and the LixiLan-O trials. The test for subgroup differences indicated that baseline HbA1c and BMI, T2DM duration and age do not modify the beneficial effect of iGlarLixi compared to iGlar on mean change in body weight (p=0.61).

Figure 5 – **Risk of hypoglycemia in the iGlarLixi group vs. the iGlar group stratified by baseline HbA1c, T2DM duration, BMI and age.** Data were retrieved from subgroup analyses of the LixiLan-L and the LixiLan-O trials. The test for subgroup differences indicated that baseline HbA1c and BMI, T2DM duration and age do not modify the effect of iGlarLixi compared to iGlar on the incidence of hypoglycemia (p=0.75). Hypoglycemia was defined as symptomatic documented plasma glucose <70 mg/dl.

Fig. 1 B&W

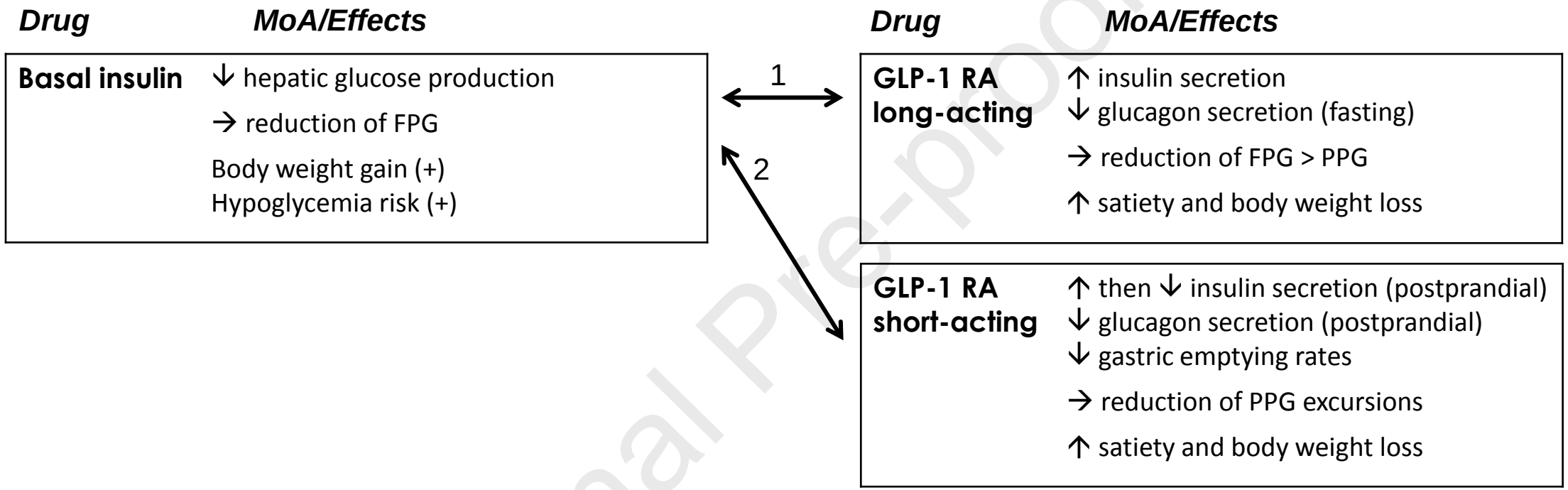

Figure 2

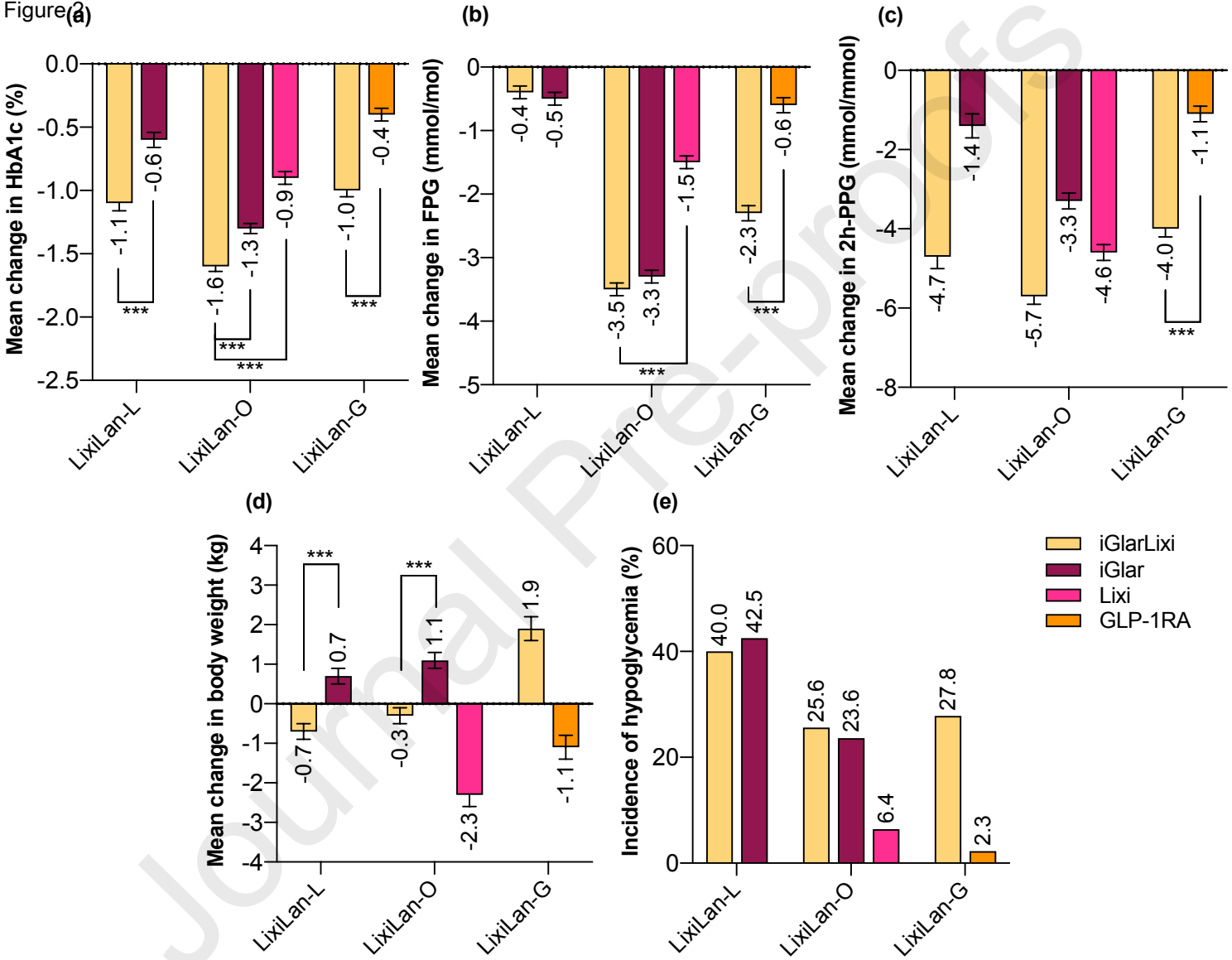

Figure 3

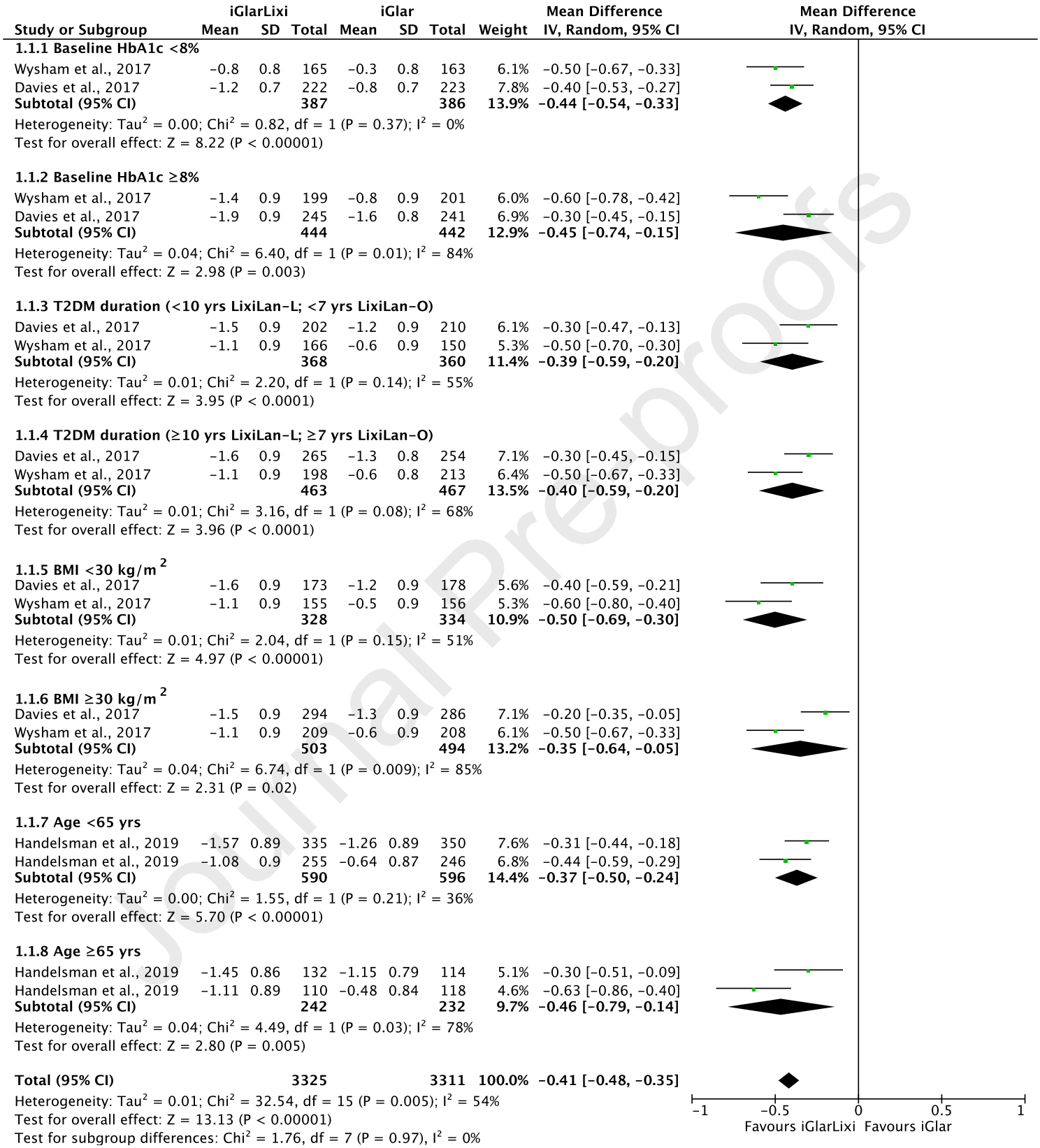

Figure 4

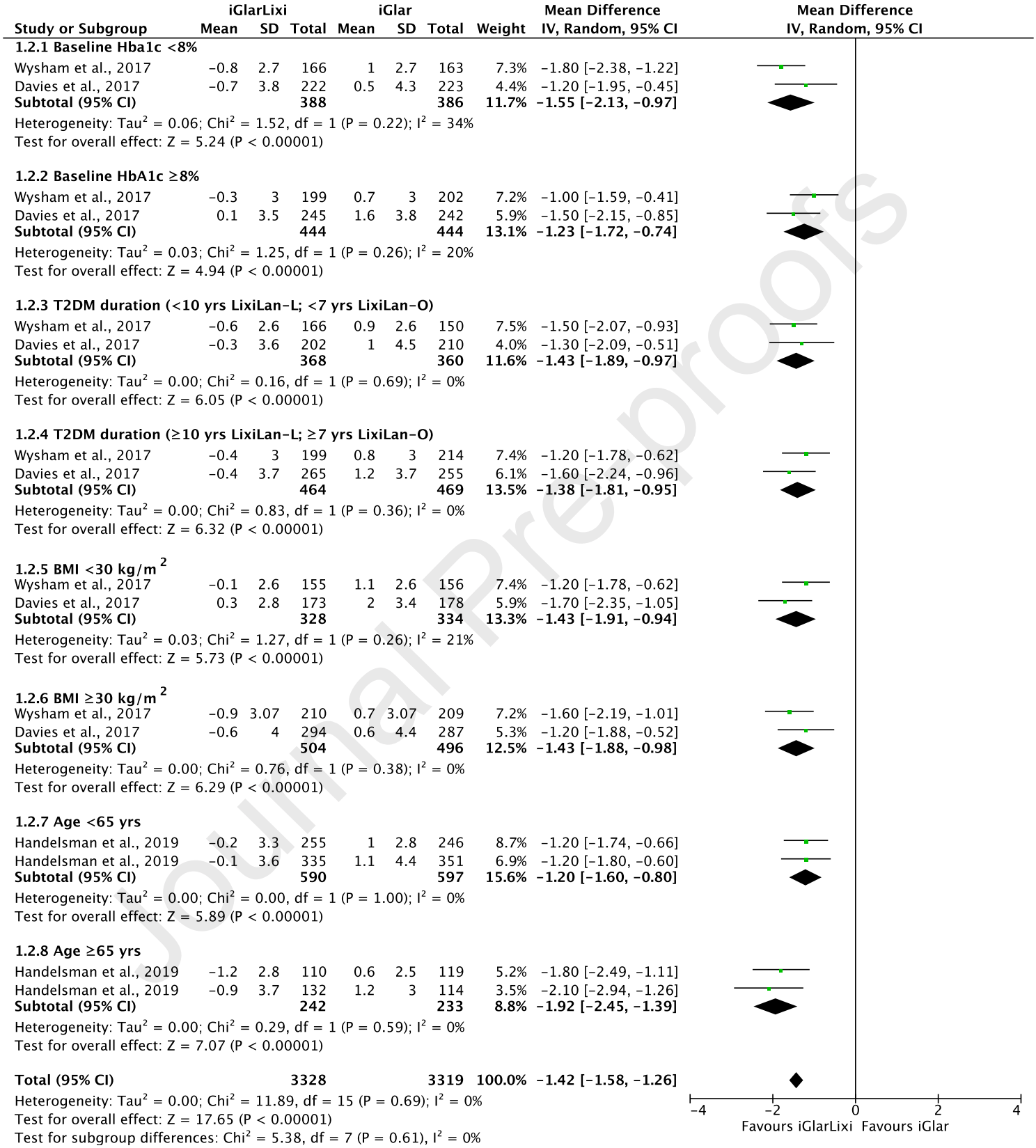

Figure 5

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
1.3.1 Baseline HbA1c <8%						
Wysham et al., 2017	54	165	69	163	5.5%	0.66 [0.42, 1.04]
Davies et al., 2017	51	222	50	223	5.6%	1.03 [0.66, 1.61]
Subtotal (95% CI)		**387**		**386**	**11.1%**	**0.83 [0.54, 1.28]**
Total events	105		119			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.89$, df = 1 (P = 0.17); $I^2 = 47\%$						
Test for overall effect: Z = 0.85 (P = 0.39)						
1.3.2 Baseline HbA1c ≥8%						
Wysham et al., 2017	92	200	86	202	7.1%	1.15 [0.77, 1.70]
Davies et al., 2017	69	247	60	244	6.8%	1.19 [0.79, 1.78]
Subtotal (95% CI)		**447**		**446**	**14.0%**	**1.17 [0.88, 1.55]**
Total events	161		146			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0\%$						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.3.3 T2DM duration (<10 yrs LixiLan-L; <7 yrs LixiLan-O)						
Wysham et al., 2017	68	166	55	150	5.4%	1.20 [0.76, 1.89]
Davies et al., 2017	43	202	40	210	4.8%	1.15 [0.71, 1.86]
Subtotal (95% CI)		**368**		**360**	**10.1%**	**1.18 [0.84, 1.64]**
Total events	111		95			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.3.4 T2DM duration (≥10 yrs LixiLan-L; ≥7 yrs LixiLan-O)						
Wysham et al., 2017	78	199	100	214	7.2%	0.73 [0.50, 1.09]
Davies et al., 2017	77	267	70	257	7.6%	1.08 [0.74, 1.59]
Subtotal (95% CI)		**466**		**471**	**14.8%**	**0.89 [0.61, 1.31]**
Total events	155		170			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.93$, df = 1 (P = 0.16); $I^2 = 48\%$						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.3.5 BMI <30 kg/m^2						
Wysham et al., 2017	74	155	78	156	5.6%	0.91 [0.59, 1.43]
Davies et al., 2017	55	174	52	179	5.4%	1.13 [0.72, 1.78]
Subtotal (95% CI)		**329**		**335**	**11.0%**	**1.01 [0.74, 1.39]**
Total events	129		130			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 0.08 (P = 0.94)						
1.3.6 BMI ≥30 kg/m^2						
Wysham et al., 2017	72	210	77	209	6.9%	0.89 [0.60, 1.33]
Davies et al., 2017	65	295	58	288	7.0%	1.12 [0.75, 1.67]
Subtotal (95% CI)		**505**		**497**	**13.9%**	**1.00 [0.76, 1.33]**
Total events	137		135			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.61$, df = 1 (P = 0.43); $I^2 = 0\%$						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.3.7 Age <65 yrs						
Handelsman et al., 2019	106	255	103	246	8.8%	0.99 [0.69, 1.41]
Handelsman et al., 2019	83	336	77	353	8.8%	1.18 [0.83, 1.68]
Subtotal (95% CI)		**591**		**599**	**17.6%**	**1.08 [0.84, 1.39]**
Total events	189		180			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 1 (P = 0.50); $I^2 = 0\%$						
Test for overall effect: Z = 0.59 (P = 0.56)						
1.3.8 Age ≥65 yrs						
Handelsman et al., 2019	40	110	52	119	3.9%	0.74 [0.43, 1.25]
Handelsman et al., 2019	37	133	33	114	3.6%	0.95 [0.54, 1.65]
Subtotal (95% CI)		**243**		**233**	**7.5%**	**0.83 [0.57, 1.22]**
Total events	77		85			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 1 (P = 0.52); $I^2 = 0\%$						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**3336**		**3327**	**100.0%**	**1.00 [0.90, 1.11]**
Total events	1064		1060			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.07$, df = 15 (P = 0.75); $I^2 = 0\%$						
Test for overall effect: Z = 0.04 (P = 0.97)						
Test for subgroup differences: $Chi^2 = 4.26$, df = 7 (P = 0.75), $I^2 = 0\%$