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Review Article

Use of glucagon-like peptide-1 receptor agonists among individuals on basal insulin requiring treatment intensification

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Abstract

As Type 2 diabetes progresses, treatment is intensified with additional therapies in an effort to manage hyperglycaemia effectively and therefore avoid complications. When greater efficacy is required, options for injectable treatments include glucagon-like peptide-1 receptor agonists and insulin, which may be added on to oral glucose-lowering treatments. Among individuals receiving long-acting basal insulin as their first injectable treatment, ~40–60% are unable to achieve or maintain their target HbA_{1c} goals. For these people, treatment intensification options are relatively limited and include the addition of short-acting prandial insulin or a glucagon-like peptide-1 receptor agonist. Glucagon-like peptide-1 receptor agonists vary in their effects, with short- and long-acting agents having a greater impact on postprandial and fasting hyperglycaemia, respectively. Studies comparing treatment intensification options have found both glucagon-like peptide-1 receptor agonists and prandial insulin to be effective in reducing HbA_{1c} concentrations; however, recipients of glucagon-like peptide-1 receptor agonists lost weight and had a greater frequency of gastrointestinal adverse events, whereas those receiving prandial insulin gained weight and had a greater incidence of hypoglycaemia. In addition to the separate administration of a glucagon-like peptide-1 receptor agonist and basal insulin, fixed-ratio combinations of a glucagon-like peptide-1 receptor agonist and basal insulin offer a single administration for both treatments but have less flexibility in dose titration than treatment with their individual components. For individuals who require treatment intensification beyond basal insulin, use of these various options allows physicians to target the individual needs of their patients for the achievement of optimal long-term glycaemic control.

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Introduction

For individuals with Type 2 diabetes, management of elevated blood glucose levels is critical to reduce the risk of complications, including microvascular and possibly cardiovascular diseases. Metformin monotherapy is usually recommended as first-line treatment [1], but the progressive nature of Type 2 diabetes can make long-term glycaemic control difficult to maintain without additional therapies. For example, the UK Prospective Diabetes Study [2] found that, 3 years after diagnosis, ~50% of people required more than one pharmacological agent because they were unable to achieve HbA_{1c} goals with monotherapy. Nine years after diagnosis, ~75% of people required combination therapy. With disease progression, worsening insulin sensitivity and progressive impairment of β-cell function make effective treatment of Type 2 diabetes more difficult; therefore, most individuals will eventually require treatment intensification to maintain glycaemic control.

Injectables such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) or basal insulin are recommended by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the American Academy of Clinical Endocrinologists as an option for treatment intensification after failure of oral monotherapy or dual therapy [1,3]. Yet, when treated with basal insulin, a common first injectable, ~40–60% of people were unable to achieve target HbA_{1c} levels after 24 weeks of treatment [4]. Options for further treatment intensification are limited and include combination injectable therapy with either a GLP-1RA or prandial insulin added on to the basal insulin regimen. In the present review, we examine the available

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What's new?

- Many patients with Type 2 diabetes require supplemental insulin as β-cell function declines.
- Treatment intensification is often required as patients are unable to achieve or maintain glycaemic control on basal insulin. For these patients, use of combination injectable treatments with different, complementary mechanisms of action can allow physicians to specifically target the glycaemic defects of their patient.
- In this rapidly changing field, this evidence-based review examines the available options for treatment intensification, including new fixed-ratio combinations of glucagon-like peptide-1 receptor agonists and basal insulin.

options for treatment intensification and data from clinical trials in this setting, and discuss the guideline-recommended treatment strategies for individuals who are unable to achieve and maintain glycaemic control with basal insulin.

A literature search was performed using the PubMed database for the following: 1) Type 2 diabetes, treatment intensification; 2) insulin, basal bolus, Type 2 diabetes; 3) liraglutide, basal insulin; 4) glucagon-like peptide-1, basal insulin; 5) insulin degludec/liraglutide fixed-ratio combination (IDegLira); 6) lixisenatide/insulin glargine fixed-ratio combination (iGlarLixi; LixiLan); and 7) fixed-dose combination, Type 2 diabetes. Searches were limited to English-language published articles on clinical trials; publications from 2000 or later were identified for the first two search terms, while the other searches were limited to publications from 2010 or later. Papers reporting results for glycaemic and body weight endpoints from clinical trials of these agents in Type 2 diabetes were selected for inclusion in the review. Relevant references listed in the bibliographies of publications identified by the literature search were also included. An additional search was performed to identify publications on the mechanism of action and treatment effects of GLP-1RAs.

Intensification process

Treatment of Type 2 diabetes should be selected based on an individual's needs, guideline recommendations, and the course of diabetes progression. Consideration must also be given to treatment cost and the potential for adverse effects, such as hypoglycaemia or weight gain. The ADA recommends that Type 2 diabetes treatment be aimed at achieving an HbA_{1c} concentration of either <53 mmol/mol (<7.0%) or <48 mmol/mol (<6.5%), depending on an individual's characteristics [5]. If initial lifestyle modifications are ineffective, oral monotherapy with metformin is the recommended first-line therapy for most people [1]. If HbA_{1c} concentration is still above target after 3 months, a second glucose-lowering medication may be added. Triple therapy is recommended if HbA_{1c} concentration remains above target after 3 months of dual therapy.

Injectable therapy with either basal insulin or a GLP-1RA may be initiated after metformin as second- or third-line treatment [1,3]. In the DURATION-3 study, which compared the GLP-1RA exenatide once weekly with titrated insulin glargine (a basal insulin) over 3 years, both treatments reduced HbA_{1c}, but the reduction was significantly greater with exenatide once weekly [–11 mmol/mol (–1.0%)] than with insulin glargine [–8 mmol/mol (–0.8%); $P = 0.03$] [6]. The proportions of individuals with HbA_{1c} at target declined over time, with 40% of exenatide once-weekly-treated participants and 33% of insulin glargine-treated participants having an HbA_{1c} concentration <53 mmol/mol (<7.0%) after 3 years. For those unable to maintain their target HbA_{1c}, combination injectable therapy with basal insulin and either a GLP-1RA or prandial insulin is recommended.

Basal insulin intensification with bolus insulin

Basal insulin, a common first injectable therapy, is typically titrated to achieve a predefined fasting glucose level. Over time, despite increasing insulin doses to counter rising fasting glucose levels, many people have difficulty achieving and maintaining HbA_{1c} goals. For example, in the Treat-to-Target trial, ~60% of overweight participants with insufficient glycaemic control [HbA_{1c} of 58–86 mmol/mol (7.5–10.0%)] with one or two oral glucose-lowering agents who received basal insulin (insulin glargine or human NPH insulin) added on to their oral therapy achieved an HbA_{1c} of ≤53 mmol/mol (≤7.0%) at 24 weeks [7]. This left ~40% of participants unable to achieve their HbA_{1c} goal and in need of treatment intensification beyond basal insulin [8]. A similar strategy was employed in the 'One Pill-One Shot' study, which compared bedtime NPH insulin and bedtime and morning insulin glargine, all added to glimepiride [9]. Again, only ~30–40% of participants achieved an HbA_{1c} concentration ≤58 mmol/mol (≤7.5%). As a consequence, additional interventions were required.

Once-daily, long-acting basal insulin improves blood glucose levels through suppression of hepatic glucose production and control of fasting glucose; however, it does not accurately mimic normal diurnal endogenous insulin secretion patterns, which separate basal and prandial insulin requirements [8]. Rapid-acting insulin analogues (e.g. insulin lispro, insulin aspart, or insulin glulisine) or premixed insulin (e.g. 70/30 aspart mix, 75/25 or 50/50 lispro mix) [1] may be used for treatment intensification for those unable to achieve appropriate postprandial glycaemic control with basal insulin [8]. In a study of participants who did not achieve glycaemic control (HbA_{1c} ≤53 mmol/mol [≤7.0%]) after 14

weeks with basal insulin glargine, prandial insulin glulisine was added once, twice or three times daily [10]. After 24 weeks, HbA_{1c} decreased similarly across groups (Table 1), but more participants achieved a target HbA_{1c} of ≤53 mmol/mol (≤7.0%) with insulin glulisine injections three times daily. In a prospective, observational study of treatment intensification in individuals with Type 2 diabetes uncontrolled on basal insulin and oral glucose-lowering therapy, participants received either basal insulin titration to target with optional addition of a rapid-acting insulin analogue at 12 or 24 weeks or addition of a rapid-acting insulin analogue at baseline [11]. After 24 weeks, HbA_{1c} reductions were similar in the two groups ($P < 0.001$ vs baseline), and similar proportions of individuals achieved an HbA_{1c} concentration of ≤53 mmol/mol (≤7.0%). The low rate of hypoglycaemic events was similar in the two groups [11]. Additional studies of insulin intensification, including AT.LANTUS, are reviewed in Abrahamson and Peters [8] and support the efficacy of this basal-bolus method; however, as with any insulin treatment, risks of weight gain, hypoglycaemia and the burden of mealtime injections, adjustments for meals, and counting carbohydrates must be considered when determining the appropriate treatment strategy.

Incretin effect and the role of glucagon

The disease course of Type 2 diabetes is characterized by progressive deterioration of β-cell function, with decreasing insulin secretion in addition to decreasing β-cell mass, as reviewed by Fonseca [12]. Increasing β-cell dysfunction over time leads to deterioration of glycaemic control over time and, hence, the need for treatment intensification. Reductions in the incretin effect and decreased α-cell function are also present in individuals with Type 2 diabetes [13,14].

The incretin effect is that in which, relative to an intravenous glucose load, an equivalent oral glucose load produces up to a 65% increase in the insulin secretory response [14]. This is attributable to the release of the gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In response to nutrient ingestion, GLP-1 receptor activation in the pancreas and throughout the body produces a glucose-dependent insulin secretory response, slows gastric emptying and improves satiety [15]. In individuals with Type 2 diabetes, the incretin effect may be reduced, if not absent, most likely because of lack of response to GIP [14]. This may be related in part to reduced β-cell mass decreasing the overall capacity of the insulin response, rather than a reduction in circulating incretin levels [14].

In addition to impaired insulin response, individuals with Type 2 diabetes have defects in the regulation of glucagon secretion [13]. In individuals with Type 2 diabetes, plasma glucagon concentrations are inappropriately elevated in the fasting state and do not decrease after carbohydrate ingestion as they do in those without Type 2 diabetes, thus contributing to both elevated fasting plasma glucose and postprandial glucose (PPG) excursions [13].

Because there are multiple pathophysiological defects in Type 2 diabetes, the use of treatments with different, complementary mechanisms of action is likely to be more effective in achieving glycaemic control [16]. While both basal insulin and incretin therapies effectively reduce fasting glucose levels, incretin therapies also reduce PPG [17] and glucagon [18]. Studies in patients with Type 1 diabetes have shown that GLP-1RAs can improve glycaemic control even among those with little to no β-cell function, suggesting that glucagon control may be particularly influential in those with long-term Type 2 diabetes [19]. Indeed, subgroup analyses of GLP-1RA clinical trial data indicate that GLP-1RAs are also effective in individuals with longer Type 2 diabetes duration, which is associated with greater deterioration of β-cell function [20–23]. Moreover, data from clinical trials, reviewed by Grandy *et al.* [24], indicate that β-cell function improves during treatment with GLP-1RAs.

Effects of GLP-1RA treatment

The GLP-1RAs are injectable glucose-lowering drugs, developed as a synthetic modification of the GLP-1-like peptide exendin-4 or GLP-1 itself [15]. In addition to binding to pancreatic GLP-1 receptors to stimulate glucose-dependent insulin release, GLP-1RAs inhibit glucagon secretion by pancreatic α cells [18] and reduce PPG excursions by slowing gastric emptying and delaying nutrient delivery to the small intestine [17]. In addition, GLP-1RAs prevent apoptosis and stimulate proliferation of β cells in animals [18]. Finally, GLP-1RAs increase satiety and reduce appetite, leading to reduced energy intake and, consequently, weight loss [15,18].

The addition of a GLP-1RA to basal insulin offers several clinical benefits over the addition of prandial insulin. By itself, the insulinotropic effects of GLP-1RAs are glucose-dependent, so the hypoglycaemia risk associated with exogenous insulin treatment is not increased [25]. In addition, whereas insulin treatment is associated with weight gain, GLP-1RA treatment is associated with weight loss [15]. A meta-analysis of 15 studies examining combination treatment of a GLP-1RA and basal insulin vs comparators such as basal insulin, bolus insulin or basal-bolus insulin found that combination GLP-1RA treatment produced a greater reduction in HbA_{1c}, weight loss, and had no increased risk of hypoglycaemia [26]. Furthermore, relative to the addition of prandial insulin to basal insulin, the weight loss associated with adding exenatide twice daily to basal insulin leads to significant improvements in the impact of weight on quality of life [27].

In two nationwide audits, the Association of British Clinical Diabetologists found that the GLP-1RAs exenatide and liraglutide were used in combination with insulin therapy among 39.6% and 36.5% of patients, respectively [28].

Table 1 Summary of selected studies examining treatment options beyond basal insulin

Citation	Background therapy	Treatment groups; randomized participants	Change in HbA_{1c}, mmol/mol (%)	Change in weight, kg	Reported hypoglycaemia	Frequency of GI AEs, % of participants			
						N	V	D	C
Davidson *et al.* 2011 [10]	Insulin glargine, two or three oral glucose-lowering medications (sulfonylureas, metformin, thiazolidinediones)	Prandial insulin glulisine (once daily); *N* = 115	–5 (–0.4)	+3.8	Participants with severe hypoglycaemia: 9	NR			
		Prandial insulin glulisine (twice daily); *N* = 113	–4 (–0.4)	+4.1	Participants with severe hypoglycaemia: 8	NR			
		Prandial insulin glulisine (three times daily); *N* = 115	–5 (–0.4)	+3.9	Participants with severe hypoglycaemia: 18*	NR			
Siegmund *et al.* 2017 [11]	Oral glucose-lowering medications, basal insulin glargine	Insulin glargine ± rapid-acting insulin analogue; *N* = 1684	–8 (–0.8)	–0.9*	Severe hypoglycaemia (1–12 weeks): 0.12% (13–24 weeks): 0.18%	NR			
		Rapid-acting insulin analogue (once daily); *N* = 518	–10 (–0.9)	–0.5	Severe hypoglycaemia (1–12 weeks): 0.0% (13–24 weeks): 0.19%	NR			
Buse *et al.* 2011 [35]	Insulin glargine, metformin, and/or pioglitazone	Exenatide twice daily; *N* = 138	–19 (–1.7)†	–1.8‡	Hypoglycaemic events per participant per year: 1.4	41‡	18‡	18‡	10‡
		Placebo; *N* = 123	–11 (–1.0)	+1.0	Hypoglycaemic events per participant per year: 1.2	8	4	8	2
Diamant *et al.* 2014 (4B Study) [27]	Insulin glargine, metformin	Exenatide twice daily; *N* = 315	–12 (–1.1)	–2.5*	Major events: 3; minor events: 332; nocturnal confirmed: 232; non-nocturnal confirmed: 103	32.4	12.4	10.8	NR
		Prandial insulin lispro (three times daily); *N* = 312	–12 (–1.1)	+2.1	Major events: 11; minor events: 870†; nocturnal confirmed: 297; non-nocturnal confirmed: 584†	1.6	1.0	5.1	NR
de Lapertosa *et al.* 2016 (4B Study; subgroup analysis of Latin American patients) [36]	Insulin glargine, metformin	Exenatide twice daily; *N* = 48	–10 (–0.9)	–0.1*	Major + minor events: 40; major events: 0; nocturnal: 26; daytime: 14	32.1	14.3	19.6	NR
		Prandial insulin lispro (three times daily); *N* = 43	–13 (–1.2)	+3.4	Major + minor events: 253; major events: 6; nocturnal: 98; daytime: 155	1.7	1.7	8.6	NR
Riddle *et al.* 2013 (GetGoal Duo-1) [37]	Insulin glargine, prior metformin ± thiazolidinediones maintained	Lixisenatide (once daily); *N* = 223	–8 (–0.7)‡	+0.3‡	Confirmed hypoglycaemia: 20.2%	27.4	9.4	6.7	NR
		Placebo (once daily); *N* = 223	–5 (–0.4)	+1.2	Confirmed hypoglycaemia: 11.7%	4.9	1.3	3.1	NR

Table 1 (*Continued*)

Citation	Background therapy	Treatment groups; randomized participants	Change in HbA_{1c}, mmol/mol (%)	Change in weight, kg	Reported hypoglycaemia	Frequency of GI AEs, % of participants			
						N	V	D	C
Seino *et al.* 2012 (GetGoal-L-Asia) [38]	Stable basal insulin (insulin glargine, insulin detemir, or NPH) ± sulfonylureas	Lixisenatide (once daily); *N* = 154	–8 (–0.8)‡	–0.4	Symptomatic hypoglycaemia: 42.9%	39.6	18.2	6.5	5.2
		Placebo (once daily); *N* = 157	+1 (+0.1)	+0.1	Symptomatic hypoglycaemia: 23.6%	4.5	1.9	2.5	2.5
Riddle *et al.* 2013 (GetGoal-L) [39]	Basal insulin ± metformin	Lixisenatide (once daily); *N* = 328	–8 (–0.7)‡	–1.8‡	Symptomatic hypoglycaemia: 26.5%	26.2	8.2	7.3	NR
		Placebo (once daily); *N* = 167	–5 (–0.4)	–0.5	Symptomatic hypoglycaemia: 21.0%	8.4	0.6	5.4	NR
Farngren *et al.* 2016 [40]	Basal insulin, metformin	Lixisenatide (once daily); *N* = 18	–5.8 (–0.5)	–1.7‡	Mild hypoglycaemia: 1 patient	38.9	NR		
		Placebo (once daily); *N* = 18	–1.0 (–0.1)	–0.6	NR	11.1	NR		
Mathieu *et al.* 2014 (BEGIN: VICTOZA ADD-ON) [41]	Insulin degludec, metformin	Liraglutide (once daily); *N* = 88	–8 (–0.7)*	–2.8†	Episodes per PYE: 1.00†	20.7	5.7	10.3	NR
		Insulin aspart (once daily); *N* = 89	–4 (–0.4)	+0.9	Episodes per PYE: 8.15	NR	NR	NR	NR
Ahmann *et al.* 2015 [42]	Insulin glargine or insulin detemir ± metformin	Liraglutide (once daily); *N* = 226	–14.2 (–1.3)‡	–3.5‡	Confirmed hypoglycaemic episodes: 127 (126 events/ 100 PYE‡)	22.2	8.9	10.7	NR
		Placebo (once daily); *N* = 225	–1.2 (–0.1)	–0.4	Confirmed hypoglycaemic episodes: 82 (83 events/100 PYE)	3.1	0.9	0.9	NR
de Wit *et al.* 2014 (ELEGANT) [43]	Insulin (basal only, basal bolus, biphasic, pump) ± metformin ± sulfonylureas	Liraglutide (once daily); *N* = 26	–8 (–0.8)*	–4.5*	Grade 1: 50.0%; Grade 2: 15.4%	42.3*	23.1	38.5*	53.8
		Background insulin therapy; *N* = 24	+0.1 (+0.01)	+0.9	Grade 1: 33.3%; Grade 2: 8.3%	12.5	4.2	25.0	8.3
de Wit *et al.* 2016 (ELEGANT 52-week results) [44]	Insulin (basal only, basal bolus, biphasic, pump) ± metformin ± sulfonylureas	Liraglutide (once daily); *N* = 25	–7 (–0.6)	+1.1	Minor hypoglycaemic events/ PYE: 2.9 (grade 1) and 0.9 (grade 2)	48.9	25.5	51.1	51.1
		Background insulin → liraglutide (once daily); *N* = 21	–7 (–0.7)	–4.3					
Seino *et al.* 2016 [45]	Insulin (basal, premixed, or basal bolus)	Liraglutide (once daily); *N* = 127	–19 (–1.7)‡	–0.3	Confirmed hypoglycaemia: 33.1%	11.0	NR	11.8	11.8
		Placebo (once daily); *N* = 130	–5 (–0.4)	+0.5	Confirmed hypoglycaemia: 27.7%	5.4	NR	3.1	1.5
Vanderheiden *et al.* 2016 [47]	Insulin (basal, premixed, or basal bolus)	Liraglutide (once daily); *N* = 35	–10 (–0.9)‡	–2.0‡	Any hypoglycaemic events/ person-month of exposure: 1.44	NR			
		Placebo (once daily); *N* = 36	0 (0.0)	+0.4	Any hypoglycaemic events/ person-month of exposure: 0.93	NR			

Table 1 (*Continued*)

Citation	Background therapy	Treatment groups; randomized participants	Change in HbA_{1c}, mmol/mol (%)	Change in weight, kg	Reported hypoglycaemia	Frequency of GI AEs, % of participants			
						N	V	D	C
Li *et al.* 2012 [46]	Insulin (glargine, NPG, premixed) ± oral medications (including sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, glinides, metformin)	Liraglutide (once daily); *N* = 42	–21 (–1.9)	–5.6	Severe: 0 participants Minor: 11.9%†	NR			
		Insulin dose increase; *N* = 42	–19 (–1.8)	+2.0	Severe: 2 participants Minor: 31.0%	NR			
Rosenstock *et al.* 2014 (Harmony 6 Study Group) [48]	Insulin glargine, prior metformin, pioglitazone and α-glucosidase inhibitors maintained	Albiglutide (once weekly); *N* = 285	–9 (–0.8)	–0.7*	Number of hypoglycaemic events (any kind): 70 (24.6%)	11.2	6.7	13.0	NR
		Prandial insulin lispro (three times daily); *N* = 281	–7 (–0.7)	+0.8	Number of hypoglycaemic events (any kind): 107 (38.1%)	1.4	1.4	4.3	NR
Gough *et al.* 2014 (DUAL-I) [56]	Metformin ± pioglitazone	IDegLira (once daily); *N* = 834	–21 (–1.9)*,†	–0.5*,†	Confirmed hypoglycaemia: 32%*,†	9	4	8	NR
		Insulin degludec (once daily); *N* = 414	–15 (–1.4)	+1.6	Confirmed hypoglycaemia: 39%	4	1	5	NR
		Liraglutide (once daily); *N* = 415	–14 (–1.3)	–0.3	Confirmed hypoglycaemia: 7%	20	8	13	NR
Gough *et al.* 2015 (DUAL-I extension) [57]	Metformin ± pioglitazone	IDegLira (once daily); *N* = 833	–20 (–1.8)*,†	–0.4*,†	Confirmed hypoglycaemic events/100 PYE: 176.7*,†	NR			
		Insulin degludec (once daily); *N* = 413	–15 (–1.4)	+2.3	Confirmed hypoglycaemic events/100 PYE: 279.1	NR			
		Liraglutide (once daily); *N* = 414	–13 (–1.2)	–3.0	Confirmed hypoglycaemic events/100 PYE: 19.1	NR			
Buse *et al.* 2014 (DUAL-II) [58]	Metformin	IDegLira (once daily); *N* = 199	–21 (–1.9)*	–2.7*	Confirmed hypoglycaemia: 24%	6.5	NR	6.5	NR
		Insulin degludec (once daily); *N* = 199	–10 (–0.9)	0.0	Confirmed hypoglycaemia: 25%	3.5	NR	3.5	NR
Lingvay *et al.* 2016 (DUAL-V) [59]	Metformin	IDegLira (once daily); *N* = 278	–20 (–1.8)*	–1.4*	Confirmed hypoglycaemic events/PYE: 2.23*	9.4	NR		
		Insulin glargine (once daily); *N* = 279	–14 (–1.1)	+1.8	Confirmed hypoglycaemic events/PYE: 5.05	1.1	NR		
Billings *et al.* 2017 (DUAL VII) [60]		IDegLira (once daily); *N* = 252	–16 (–1.5)	–0.9	Hypoglycaemic events/PYE: 1.1	NR	NR	NR	NR
		Insulin glargine (once daily) + insulin aspart (prandial); *N* = 254	–16 (–1.5)	+2.6	Hypoglycaemic events/PYE: 8.2	NR	NR	NR	NR
Rosenstock *et al.* 2016 (LixiLan PoC study) [51]	Metformin	LixiLan (once daily); *N* = 161	–20 (–1.8)*	–1.0*	Documented symptomatic hypoglycaemic events: 35 (21.7%)	7.5	2.5	3.1	1.9
		Insulin glargine (once daily); *N* = 162	–18 (–1.6)	+0.5	Documented symptomatic hypoglycaemic events: 37 (22.8%)	0.0	0.6	3.7	0.0

Table 1 (*Continued*)

Citation	Background therapy	Treatment groups; randomized participants	Change in HbA_{1c}, mmol/mol (%)	Change in weight, kg	Reported hypoglycaemia	Frequency of GI AEs, % of participants			
						N	V	D	C
Aroda *et al.* 2016 (LixiLan-L study) [53]	Metformin	LixiLan (once daily); *N* = 367	–14 (–1.1)*	–0.7*	Documented symptomatic hypoglycaemia: 40% (3.03 events/PYE)	10.4	3.6	4.4	NR
		Insulin glargine (once daily); *N* = 369	–7 (–0.6)	+0.7	Documented symptomatic hypoglycaemia: 42.5% (4.22 events/PYE)	0.5	0.5	2.7	NR
Rosenstock *et al.* 2016 (LixiLan-O study) [52]	Metformin	LixiLan (once daily); *N* = 469	–18 (–1.6)*,†	–0.3*	Documented symptomatic hypoglycaemia: 25.6% (1.4 events/PYE)	9.6	3.2	9.0	NR
		Insulin glargine (once daily); *N* = 467	–14 (–1.3)	+1.1	Documented symptomatic hypoglycaemia: 23.6% (1.2 events/PYE)	3.6	1.5	4.3	NR
		Lixisenatide (once daily); *N* = 234	–10 (–0.9)	–2.3	Documented symptomatic hypoglycaemia: 6.4% (0.3 events/PYE)	24.0	6.4	9.0	NR

AE, adverse event; C, constipation; D, diarrhoea; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; N, nausea; NR, not reported; PoC, proof of concept; PYE, person-years of exposure; V, vomiting.
*$P < 0.05$ vs insulin comparator. †$P < 0.05$ vs GLP-1RA comparator. ‡$P < 0.05$ vs placebo.

At the time of the exenatide audit (2007–2009), exenatide had not yet received regulatory approval for use with basal insulin. Since its approval, the ADA and EASD have included the addition of a GLP-1RA to basal insulin among their recommendations in the 2015 update to their Position Statement, noting that the lower risk of hypoglycaemia, need for fewer injections, and associated weight loss may make GLP-1RAs more appropriate than prandial insulin for some individuals [1]. This recommendation includes agents approved in both the USA and Europe: exenatide twice daily, exenatide once weekly, liraglutide, albiglutide, dulaglutide and lixisenatide.

The different GLP-1RAs can be further subcategorized by their duration of exposure. Exenatide twice daily and lixisenatide (once daily), two short-acting GLP-1RAs, are typically dosed before breakfast with the second exenatide twice-daily dose given before dinner [29]. The resulting short-term increase in plasma peptide levels reduces PPG excursions via delayed gastric emptying, which reduces the necessary insulin response [17]. Postprandial glucagon release is reduced and postprandial insulin release is enhanced [30]; however, these GLP-1RAs are less available during fasting states and are therefore less effective for reducing fasting measures. In contrast, for the long-acting GLP-1RAs exenatide once weekly, liraglutide, albiglutide and dulaglutide, effects on gastric emptying are not as strong as their short-acting counterparts [31] or decline over time [32], probably as a result of the continuous GLP-1RA exposure causing tachyphylaxis [33], leading to less pronounced PPG reductions [34]. Instead, these agents appear to reduce HbA_{1c} concentration through sustained increase in fasting insulin [34], suppression of fasting glucagon [31], and subsequently lower fasting glucose levels. Several studies have compared the effects of long- vs short-acting GLP-1RAs. For example, in the LEAD-6 study, when compared with recipients of exenatide twice daily, liraglutide recipients had a greater reduction in HbA_{1c} and fasting glucose levels, similar weight loss, and a lesser reduction in PPG increment after breakfast and dinner [34]. Similarly, the DURATION-1 study found that exenatide once weekly was associated with a significantly greater reduction in HbA_{1c} and fasting glucose than exenatide twice daily, with similar reductions in body weight [31]; the reduction in 2-h PPG was significantly greater with exenatide twice daily. As such, the specific fasting or postprandial effects of long- vs short-acting GLP-1RAs may be exploited for targeted treatment according to a person's individual characteristics.

Treatment intensification of basal insulin with GLP-1RAs

Several studies have examined the safety and efficacy of GLP-1RAs in combination with insulin (Table 1); as a class, these agents are effective in reducing HbA_{1c} and body weight, with a low risk of hypoglycaemia but increased rates of gastrointestinal adverse events (AEs) vs comparators. A randomized, placebo-controlled trial compared the effects of short-acting exenatide twice daily with placebo, both added to optimized insulin glargine, in participants with Type 2 diabetes unable to achieve glycaemic control [HbA_{1c} of 54–91 mmol/mol (7.1–10.5%)] with insulin glargine [35]. After 30 weeks, exenatide twice daily reduced HbA_{1c} significantly ($P < 0.001$) more than placebo. In addition, 60% of participants treated with exenatide twice daily achieved an HbA_{1c} of ≤53 mmol/mol (≤7.0%), compared with 35% of placebo-treated participants. Body weight decreased with exenatide twice-daily treatment, whereas it increased with placebo ($P < 0.001$ for difference). There was no between-group difference in the number of hypoglycaemic events per participant per year. Nausea, diarrhoea, vomiting, headache and constipation occurred more frequently with exenatide twice daily than with placebo. The 4B study directly compared the effects of exenatide twice daily with those of prandial insulin among participants who did not achieve sufficient glycaemic control [HbA_{1c} ≤53 mmol/mol (≤7.0%)] after a 12-week basal insulin optimization phase [27]. Participants were randomized to receive either exenatide twice daily or prandial insulin lispro, both added to titrated insulin glargine and metformin, for 30 weeks. At endpoint, HbA_{1c} was reduced in both groups and exenatide twice daily was found to be non-inferior to insulin lispro. Participants receiving exenatide twice daily lost weight, whereas those receiving insulin lispro gained weight ($P < 0.001$ from baseline). Fasting glucose concentration was significantly reduced with exenatide twice daily but not with insulin lispro, and PPG values were similar except after lunch. Minor and confirmed non-nocturnal hypoglycaemia occurred less frequently with exenatide twice daily than with insulin lispro, with two exenatide twice-daily-treated participants and seven insulin lispro-treated participants experiencing at least one major hypoglycaemic episode. Nocturnal hypoglycaemia was similar for exenatide twice daily and insulin lispro. Gastrointestinal AEs, including nausea, vomiting and diarrhoea, occurred more frequently with exenatide twice-daily treatment. A subanalysis of 4B study participants from Argentina and Mexico showed similar results to the main study (Table 1) [36].

Studies of lixisenatide (also short-acting) have found a similar pattern of results (Table 1). In the GetGoal Duo-1 study, a 24-week study of lixisenatide, participants unable to achieve glycaemic control after 12 weeks with titrated insulin glargine were randomized to receive either lixisenatide or placebo, both added to insulin glargine [37]. HbA_{1c} decreased significantly ($P < 0.0001$) more with lixisenatide than with placebo. Body weight increased in both groups, but the increase was significantly ($P = 0.0012$) less with lixisenatide. Both hyperglycaemia and gastrointestinal AEs occurred more frequently with lixisenatide than with placebo. In the GetGoal-L-Asia study, which had a similar design [38], HbA_{1c} was reduced with lixisenatide but

increased with placebo ($P < 0.0001$). There was a numerical decrease in body weight with lixisenatide compared with an increase in body weight with placebo. Lixisenatide recipients had an overall higher incidence of gastrointestinal AEs and hypoglycaemic events. The GetGoal-L study examined the addition of lixisenatide to an established, stable basal insulin regimen [39]. Reductions in HbA_{1c} and body weight were significantly greater with lixisenatide ($P = 0.0002$ and $P < 0.0001$, respectively). The frequency of hypoglycaemia was similar in the two groups and, as in the other two studies, participants receiving lixisenatide experienced more gastrointestinal AEs. In a single-centre, randomized, double-blind, placebo-controlled crossover study of lixisenatide that investigated treatment intensification in individuals with an HbA_{1c} of 61 mmol/mol (7.7%) despite basal insulin and metformin treatment, 6 weeks of lixisenatide treatment resulted in reductions in HbA_{1c} and body weight vs placebo ($P = 0.043$) [40].

Across the studies of short-acting GLP-1RAs added to basal insulin, improvements in measures of PPG control were consistently observed, either via self-monitored blood glucose measures [27,35] or a standardized meal test [37–39]. Given that short-acting GLP-1RAs tend to exhibit greater postprandial control than long-acting GLP-1RAs [31], short-acting GLP-1RAs may be an appropriate choice for individuals on basal insulin exhibiting a postprandial glycaemic deficit. In contrast, long-acting GLP-1RAs may offer greater benefit to individuals requiring improvements in fasting glycaemic control.

Long-acting GLP-1RAs have also been found to improve glycaemic control and body weight, without increasing hypoglycaemia risk (Table 1). The BEGIN: VICTOZA ADD-ON study compared the effects of once-daily insulin aspart with once-daily liraglutide, added to basal insulin degludec and metformin, among participants with HbA_{1c} ≥53 mmol/mol (≥7.0%) despite treatment with basal insulin [41]. At endpoint (26 weeks), a significantly ($P = 0.0024$) greater reduction in HbA_{1c} was seen with liraglutide than with insulin aspart. Significantly ($P < 0.0001$) greater weight loss was observed among participants treated with liraglutide compared with those receiving insulin aspart. The rate of confirmed hypoglycaemia was significantly ($P < 0.0001$) lower with liraglutide than with insulin aspart, while gastrointestinal AEs occurred more frequently with liraglutide. Another 26-week study that compared liraglutide with placebo, both added to basal insulin with or without metformin, found that both HbA_{1c} and body weight decreased significantly ($P < 0.0001$) more with liraglutide than with placebo [42]. Gastrointestinal AEs were more common with liraglutide relative to placebo, as was confirmed hypoglycaemia ($P = 0.04$). The ELEGANT study found that adding liraglutide to a standard insulin regimen (basal only, basal bolus, biphasic, or pump therapy) for 26 weeks significantly ($P < 0.001$) reduced HbA_{1c} concentration relative to continuing standard insulin treatment [43]. Furthermore, body weight decreased rather than increased with liraglutide compared with standard therapy ($P < 0.001$ for difference). The frequency of hypoglycaemia was similar for both treatments, but gastrointestinal AEs were more common with liraglutide. A 52-week extension study of ELEGANT showed that the improvements in HbA_{1c} and body weight seen in the core study were sustained in the long term (Table 1) [44]. In a separate study of Japanese participants with Type 2 diabetes, 36 weeks of treatment with liraglutide added to an insulin regimen resulted in a significantly ($P < 0.0001$) greater reduction in HbA_{1c} than placebo and weight loss rather than weight gain [45]. Gastrointestinal AEs were more common with liraglutide, and there was no difference in the frequency of confirmed hypoglycaemia. In a study of Chinese participants who either added liraglutide to an existing insulin regimen or increased their current insulin dose to achieve glycaemic targets, both groups had a significant ($P < 0.01$) reduction in HbA_{1c} relative to baseline; however, the liraglutide-added group lost weight ($P < 0.01$) while the insulin-increasing group gained weight ($P < 0.01$) [46]. Minor hypoglycaemia occurred significantly ($P = 0.033$) more often among the insulin-increasing group, whereas AEs were more common in the liraglutide-added group ($P = 0.028$; most commonly gastrointestinal). In another study, 71 individuals with uncontrolled Type 2 diabetes despite the use of insulin 1.5 U/kg/day were randomized to receive liraglutide or placebo for 6 months [47]. After 6 months, liraglutide-treated participants had a significant ($P < 0.001$) reduction in HbA_{1c} from baseline, while HbA_{1c} remained unchanged among placebo recipients. Body weight decreased from baseline in the liraglutide group and increased in the placebo group, leading to a significant ($P = 0.02$) between-group difference favouring liraglutide. While hypoglycaemia rates were higher with liraglutide than with placebo in the first month of treatment ($P < 0.01$), they were similar between groups over the entire follow-up period (Table 1) [47].

A 26-week study (HARMONY 6) of the long-acting GLP-1RA albiglutide had similar results (Table 1) [48]. Participants with Type 2 diabetes inadequately controlled with basal insulin were randomized to receive albiglutide or prandial insulin lispro. After 26 weeks, the change in HbA_{1c} was similar in the two groups, confirming non-inferiority of either treatment. As with other GLP-1RAs, albiglutide was associated with weight loss, whereas insulin lispro was associated with weight gain, and there was a significant ($P < 0.0001$) difference in the change in body weight between the two groups. The incidence of documented pre-rescue hypoglycaemia was almost twice as high for insulin lispro as for albiglutide, while gastrointestinal AEs occurred more frequently with albiglutide than with insulin lispro.

The use of GLP-1RAs for treatment intensification in individuals with Type 2 diabetes receiving basal insulin has also been evaluated in 'real-world' studies. An analysis of health insurance claims data found that the reduction in

HbA_{1c} after adding a GLP-1RA was similar to that for adding prandial insulin and greater than that with an increased basal insulin dose [49]. Hypoglycaemia rates were lower for GLP-1RA treatment than for either added prandial insulin or increased basal insulin dose. Another analysis of claims data also found comparable reductions in HbA_{1c} for a GLP-1RA or prandial insulin added to basal insulin [50]. While overall hypoglycaemia rates were similar, hospitalization for hypoglycaemia was more frequent among the prandial insulin cohort.

Fixed-ratio formulations

More recently, two additional fixed-ratio, single-injection products containing both a GLP-1RA and a basal insulin have been studied (Table 1). IGlarLixi (previously called LixiLan), which combines the short-acting GLP-1RA lixisenatide with insulin glargine, is approved in the USA and Europe [51]. Participants randomized to treatment with either iGlarLixi or insulin glargine for 24 weeks in a proof-of-concept trial both had HbA_{1c} reductions; however, the reduction with iGlarLixi was superior to that with insulin glargine ($P = 0.013$). Furthermore, body weight decreased with iGlarLixi but increased with insulin glargine alone ($P < 0.0001$ for difference). The frequency of hypoglycaemic events was similar for each treatment. A subsequent trial, the randomized, open-label LixiLan-O study, investigated the efficacy and safety of iGlarLixi vs insulin glargine and lixisenatide administered separately among participants ($n = 1170$) with Type 2 diabetes who were uncontrolled on metformin with or without a second oral glucose-lowering agent (Table 1) [52]. After 30 weeks, individuals receiving iGlarLixi had significantly ($P < 0.0001$) greater reductions in HbA_{1c} than those receiving insulin glargine or lixisenatide, and significantly ($P < 0.0001$) more participants achieved an HbA_{1c} of <53 mmol/mol (<7.0%). IGlarLixi was statistically superior to lixisenatide and non-inferior to insulin glargine for HbA_{1c} reduction. Body weight decreased among iGlarLixi and lixisenatide recipients but increased with insulin glargine, with a significant ($P < 0.0001$) between-group difference for iGlarLixi vs insulin glargine. The number of hypoglycaemic events was similar with iGlarLixi and insulin glargine; recipients of lixisenatide had the lowest number of hypoglycaemic events [52]. The LixiLan-L study investigated the use of iGlarLixi among individuals who were inadequately controlled on basal insulin with ≤2 oral glucose-lowering drugs (Table 1) [53]. After 30 weeks of open-label treatment, reductions in HbA_{1c} with iGlarLixi were significantly ($P < 0.0001$) greater than those with insulin glargine alone, and more individuals receiving iGlarLixi than insulin glargine achieved HbA_{1c} <53 mmol/mol (<7.0%; $P < 0.0001$). IGlarLixi was superior to insulin glargine for the change in HbA_{1c}. Mean body weight decreased in iGlarLixi recipients but increased in insulin glargine recipients (between-group difference, 1.4 kg; $P < 0.0001$), and the number of hypoglycaemic events was similar in the two groups [53]. In both studies, the improvement in glycaemic control with iGlarLixi vs the individual therapies was consistent regardless of baseline HbA_{1c}, BMI or diabetes duration [54,55].

IDegLira, which combines insulin degludec and the long-acting GLP-1RA liraglutide, was recently approved for use in Europe and the USA. The DUAL-I trial compared IDegLira (insulin degludec 100 U/ml plus liraglutide 3.6 mg/ml) with its components, insulin degludec (100 U/ml) and liraglutide (6 mg/ml), plus metformin and pioglitazone at pre-trial doses in participants with Type 2 diabetes (Table 1) [56]. Compared with liraglutide, IDegLira resulted in a greater HbA_{1c} reduction (superiority, $P < 0.0001$), a higher rate of hypoglycaemia ($P < 0.0001$) and less weight loss ($P < 0.0001$). Compared with insulin degludec, IDegLira had a similar reduction in HbA_{1c} (non-inferiority, $P < 0.0001$), lower rates of hypoglycaemia ($P = 0.0023$), and weight loss rather than weight gain ($P < 0.0001$). A 26-week extension confirmed that improvements in glycaemic control and body weight, and low hypoglycaemia rates, were maintained in the long term (Table 1) [57]. In a second trial (DUAL-II), IDegLira was compared with insulin degludec in participants who had not achieved adequate glycaemic control on basal insulin alone [58]. For this study, IDegLira recipients had a significantly ($P < 0.0001$) greater reduction in HbA_{1c} compared with those receiving insulin degludec. Body weight decreased with IDegLira but was unchanged with insulin degludec, and rates of confirmed hypoglycaemia were similar. In the DUAL-V study that investigated the non-inferiority of IDegLira vs continued insulin glargine titration among individuals with Type 2 diabetes uncontrolled on insulin glargine plus metformin, 26 weeks of treatment with IDegLira was non-inferior to insulin glargine uptitration regarding effects on HbA_{1c} levels; IDegLira recipients had greater HbA_{1c} reductions than individuals receiving insulin glargine uptitration ($P < 0.001$; Table 1) [59], as well as weight loss vs weight gain in the uptitration group ($P < 0.001$). IDegLira recipients also had fewer hypoglycaemia events per person-year of exposure vs individuals receiving insulin glargine uptitration (Table 1) [59]. Results from the DUAL VII study showed that IDegLira was non-inferior to basal-bolus insulin treatment (insulin glargine plus insulin aspart) in reducing HbA_{1c} ($P < 0.0001$ for non-inferiority) among individuals with inadequate glycaemic control on insulin glargine plus metformin (Table 1) [60]. Similar proportions of participants achieved HbA_{1c} goals of <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%) with both treatments. However, IDegLira recipients lost weight whereas the basal-bolus insulin group gained weight ($P < 0.0001$ for difference), and hypoglycaemic episodes were less frequent with IDegLira than with basal-bolus insulin ($P < 0.0001$).

Although the fixed-ratio approach of iGlarLixi and IDegLira offers some potential benefits, the treatment simplification may be limited for individuals who are already

taking multiple medications for comorbid conditions [61]. In addition, people begin treatment with IDegLira on a lower dose and uptitrate, and individuals may require higher doses than available in combination or otherwise risk receiving a suboptimal dose of GLP-1RA treatment [62]. Further, in the 2014 assessment report, the European Medicines Agency provided a divergent position of some member country agencies for IDegLira, citing the lack of dosing flexibility and the potential unnecessary exposure to combination therapy among individuals who do not achieve glycaemic control with oral therapy as compared to using basal insulin and a GLP-1RA separately [63]. Patients may achieve greater benefits by utilizing the optimal dose of a GLP-1RA and the addition of insulin, titrated as needed. With the availability of weekly dosing for some GLP-1RAs, this regimen requires only one additional injection per week. Furthermore, the fixed-dose approach provides less flexibility for dose titration because only the available dose combinations can be used, and physicians may be unable to identify which component treatment is responsible for any AEs that occur.

Discussion

Achieving and maintaining glycaemic control are important in reducing the risk of complications associated with Type 2 diabetes; however, over time, treatment intensification is often necessary to counteract the progressive nature of Type 2 diabetes and maintain glycaemic targets. For individuals unable to achieve glycaemic control with a single injectable, use of a combination injectable treatment can target specific glycaemic defects. When used with basal insulin, both GLP-1RAs and prandial insulin reduce HbA_{1c} and increase the proportion of individuals achieving HbA_{1c} targets. Prandial insulin, however, is generally associated with weight gain and a higher risk of hypoglycaemia. By contrast, adding a GLP-1RA to basal insulin rapidly improves glycaemic control with less titration than insulin or a fixed-ratio combination of basal insulin and a GLP-1RA [56], requires fewer injections, and is associated with weight loss and a low risk of hypoglycaemia. For some, these properties may make the addition of a GLP-1RA to basal insulin preferable to prandial insulin. Furthermore, the earlier that GLP-1RAs are used, the sooner the individual can obtain the advantages of GLP-1RA-induced weight loss.

When choosing which GLP-1RA to add to basal insulin, specific properties of long- vs short-acting GLP-1RAs allow further treatment individualization. Short-acting GLP-1RAs are generally more effective at targeting postprandial hyperglycaemia and may be better suited for individuals with a primary postprandial deficit, whereas long-acting GLP-1RAs are generally more effective for reducing fasting hyperglycaemia and may be a better option for those with poor fasting control. For those with an overall high HbA_{1c} despite basal insulin treatment, the addition of a short-acting GLP-1RA could be an initial option for treatment intensification. Fixed-ratio combinations allow individuals to administer a GLP-1RA and insulin with a single injection, which may be preferable for some people, but they also allow less dosing flexibility. As Type 2 diabetes progresses and treatment is intensified, physicians should consider the individual needs and preferences of their patients, balancing the risks and benefits of the available treatment options to develop a management plan that provides their patients with the greatest clinical benefit.

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Competing interests

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