Diabetes Management

The place of IDegLira in the management of patients with Type 2 diabetes

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Practice points

- Insulin initiation and intensification are often severely delayed, partly due to the risks of weight gain and hypoglycemia.
- Combining liraglutide and insulin degludec in a once-daily, fixed-ratio injection, can be used as an add-on when OAD therapy alone or combined with a GLP-1 receptor agonist or basal insulin does not provide adequate blood glucose control.
- IDegLira can offer lowering of HbA_{1c} without increasing hypoglycemia (vs basal insulin alone) and with no mean weight change, or even weight loss.

Type 2 diabetes mellitus is a progressive disease and this means that treatment intensification is needed to achieve glycemic goals and, for many patients, insulin will ultimately be needed. There is the potential for insulin to achieve any glycemic target, however, its initiation and up-titration is frequently delayed, partly due to the attendant weight gain and risk of hypoglycemia. Several clinical trials have demonstrated that combining a GLP-1 receptor agonist with basal insulin produces significant reductions in HbA_{1c} without substantially increasing hypoglycemia or promoting weight gain. A once-daily coformulation of ultra-long-acting basal insulin degludec and the GLP-1 analog liraglutide, termed 'IDegLira', has now been developed for patients with Type 2 diabetes. Data from two Phase III clinical trials are encouraging, demonstrating marked HbA_{1c} reductions with weight loss, low levels of hypoglycemia and limited gastrointestinal side effects. The types of patients that may benefit from a fixed-ratio combination such as IDegLira are discussed here, as are future developments.

KEYWORDS
• combination therapy
• GLP 1 receptor agonist
• IDegLira • Xultophy

Background

The pathophysiology of Type 2 diabetes (T2DM) is characterized by a variable combination of insulin resistance, impaired insulin secretion and hyperglucagonemia. Additional features of the 'ominous octet' of defects in T2DM have also been well described [1]. The progressive nature of T2DM necessitates intensification of treatment to maintain glycemic control over time. Since none of the currently available therapies have been shown to modify the underlying pathophysiology of T2DM, many patients will ultimately need insulin replacement [2].

The European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) consensus position statement focuses on an HbA_{1c} of <53 mmol/mol (<7.0%) with initiation of insulin therapy (typically basal insulin) as dual or triple therapy, if a patient does not achieve or maintain target after around 3 months [3]. In England and Wales, when dual oral therapy does not achieve target, NICE recommends intensification with either a third oral agent, a GLP-1 receptor agonist (RA) or basal insulin in patients with an HbA_{1c} of ≥58 mmol/mol (≥7.5%) [4].

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However, these guidelines do not seem to be being followed.

Clinical inertia

A recent cohort study of 81,573 people with T2DM reported that in patients with an HbA_{1c} ≥58 mmol/mol (≥7.5%), the median time to insulin initiation in the UK was over 6 years [5]. Regarding insulin intensification, another primary care database analysis reported that intensification of basal insulin treatment occurred in only 33% of UK patients, despite most having suboptimal glycemic control [6]. This treatment inertia is not confined to the UK: a large observational study (n = 17,374) of ten countries reported that mean HbA_{1c} at insulin initiation ranged from 67 mmol/mol (8.3%; China) up to 84 mmol/mol (9.8%; UK), with a mean across the study of 74 mmol/mol (8.9%) [7]. Both patient and physician factors contribute to this inertia, and these include fear of hypoglycemia, weight gain and a reluctance to inject. The resource implications of more complex therapeutic regimes also impact upon physician decision-making. Although recent guidance from the ADA and EASD [3] recognizes cases where it is reasonable to aim for more modest glycemic targets such as in older, more frail patients who have a high cardiovascular disease burden. The patients included in these studies had a reasonably short duration of diabetes and a relatively young mean age, suggesting that clinical inertia is a fairly common occurrence. Ultimately, failure to optimize glycemic control increases the incidence of complications, which largely determine the economic impact of T2DM. The prospect of using combinations of newer therapies, which can offer the same potential efficacy of insulin but with an improved risk/benefit profile and which are relatively straightforward to use may help to overcome this inertia [8].

Therapy combinations

When patients with T2DM have insulin initiated, metformin is typically continued, as there is less weight gain when these two classes of antidiabetic drugs are used together [9]. In contrast, the insulin secretagogues (sulfonylureas and glinides, such as repaglinide) are usually discontinued due to increased risk of hypoglycemia and minimal glycemic benefit [10]. Similarly, clinicians generally discontinue or reduce the dose of pioglitazone so as to reduce the risk of edema and weight gain seen in combination with insulin [3,10]. The more recently licensed noninsulin therapies, namely GLP-1 RAs, DPP-4 inhibitors and SGLT-2 inhibitors, are continued after insulin initiation, and can also be added to existing insulin therapy as an alternative approach to insulin intensification [3]. Intensification with insulin (either prandial or premix) involves more frequent injections, additional blood testing and potentially complex titration regimes. Details of the studies combining insulin and other antidiabetic medications described in this review are summarized in **Table 1**.

SGLT-2 inhibitors & insulin

The SGLT-2 inhibitors form the newest class of oral antidiabetic treatment for T2DM and, as a result, they have only limited inclusion in treatment algorithms. However, the three approved agents – dapagliflozin, canagliflozin and empagliflozin – all have broad indications, including combination with insulin [11–13]. In Phase III studies, the addition of an SGLT-2 inhibitor to relatively advanced insulin regimens (patients taking mean daily insulin doses of 78–92 units) resulted in significant improvements in HbA_{1c} and weight [14–16]. Typical improvements in HbA1c were of the order of 11 mmol/mol (1.0%). However, a proportion of patients will fail to achieve target HbA_{1c}, also there was a higher frequency of genital fungal infection and hypoglycemia, compared with placebo [14–16]. The US FDA has also recently warned of a possible risk of diabetic ketoacidosis (DKA) with this combination therapy, which can potentially be precipitated in insulinopenic patients by dehydrating illness or infection.

DPP-4 inhibitors & insulin

The EASD/ADA position statement [3] sanctions the use of DPP-4 inhibitors in combination with insulin therapy and Phase III trials have investigated the use of all five DPP-4 inhibitors as add-on to insulin [17–21]. A significantly greater fall in HbA_{1c} was observed versus placebo but the reductions were modest (between 7 and 9 mmol/mol [0.6–0.8%]) considering the high baseline HbA_{1c} (67–78 mmol/mol [8.3–9.3%]). As a result of this, mean HbA_{1c} remained above target levels at the end of studies (61–70 mmol/mol [7.7–8.6%]). Despite the reductions in HbA_{1c}, the vast majority of patients had an HbA_{1c} above 53 mmol/mol at the end of the trials [18,19]. The addition of

Table 1. Summary of key data from studies cited in this review.

Study (year)	Study duration (weeks)	Treatment arms (n)	Ref.
EMPA-REG MDI trial (2014)	52	MDI insulin ± metformin plus: – Empagliflozin 10 mg (186) – Empagliflozin 25 mg (189) – Placebo (188)	[14]
CANVAS substudy (2012)	18	Insulin (>30 units/day) plus: – Placebo (565) – Canagliflozin 100 mg (566) – Canagliflozin 300 mg (587)	[15]
Dapagliflozin 006 study group (2012)	24 (24 extension)	Insulin (≥30 units/day) ± 0–2 oral hypoglycemic agents plus: – Dapagliflozin 2.5 mg (202) – Dapagliflozin 5 mg (212) – Placebo (197)	[16]
Rosenstock *et al.* (2009)	26	Stable insulin therapy ± metformin plus: – Alogliptin 12.5 mg (131) – Alogliptin 25 mg (129) – Placebo (130)	[17]
Vilsbøll *et al.* (2010)	24	Long-/intermediate-/premixed insulin ± metformin plus: – Sitagliptin 100 mg (322) – Placebo (319)	[18]
Barnett *et al.* (2012)	52	Stable insulin therapy ± metformin plus: – Saxagliptin 5 mg (244) – Placebo (124)	[19]
Yki-Järvinen *et al.* (2013)	≥52	Basal insulin ± metformin ± pioglitazone plus: – Linagliptin 5 mg (631) – Placebo (630)	[20]
Kothny *et al.* (2013)	24	Stable insulin therapy ± metformin plus: – Vildagliptin 50 mg b.i.d. (228) – Placebo (221)	[21]
DeVries *et al.* (2011)	26	Liraglutide 1.8 mg + metformin (161) versus liraglutide 1.8 mg + metformin + insulin determir (162)	[22]
Aroda *et al.* (2014)	26	Liraglutide 1.8 mg + metformin plus: – Insulin degludec (174) – Placebo (172)	[25]
Buse *et al.* (2011)	30	Insulin glargine ± metformin ± pioglitazone plus: – Exenatide 10 μg b.i.d. (138) – Placebo (123)	[26]
GetGoal-L (2013)	24	Basal insulin ± metformin plus: –Lixisenatide 20 μg (328) – Placebo (167)	[27]
GetGoal-Duo 1 (2013)	24	Insulin glargine + metformin ± TZDs plus: – Lixisenatide 20 μg (223) – Placebo (223)	[28]
BEGIN: VICTOZA ADD-ON (2014)	52 (52 extension)	Insulin degludec + metformin plus: – Liraglutide 1.2–1.8 mg (88) – Insulin aspart (89)	[29]
Harmony six study group (2014)	26	Insulin glargine ± oral agents plus: – Albiglutide 30–50 mg/weekly (282) – Thrice-prandial lispro (281)	[30]
LIRA-ADD2BASAL (2014)	26	Stable insulin dose ± metformin plus: – Liraglutide 1.8 mg (226) – Placebo (225)	[31]
4B study group (2014)	30	Insulin glargine + metformin plus: – Exenatide 10–20 μg/day (315) – Thrice-daily insulin lispro (312)	[32]

b.i.d.: Twice daily; TZD: Thiazolidinedione.

a DPP-4 inhibitor to existing insulin therapy was generally weight neutral (similar to placebo) and hypoglycemia was experienced by 8–27% of patients (vs 7–24% placebo).

GLP-1 RAs & insulin

The use of GLP-1 RAs in combination with basal insulin (in triple therapy with metformin) is recommended in the EASD/ADA position statement [3]. There exists the option both for adding basal insulin to existing metformin and GLP-1 RA therapy or adding a GLP-1 RA to metformin and basal insulin [3]. While this combination has only recently been licensed for some GLP-1 RAs, the combination has been widely used in secondary care in the UK [22,23]. The Association of British Clinical Diabetologists (ABCD) audited the early use of both exenatide twice-daily (2007–2009) and liraglutide (2009–2011) and reported that over 36% of GLP-1 RA use was in the unlicensed combination with insulin [22,23].

Insulin add-on to GLP-1 RAs

There have been two reported studies which examined the addition of the GLP-1 RA, liraglutide, to oral antidiabetic therapy, followed by basal insulin in those patients who did not achieve target HbA_{1c} (both studies <53 mmol/mol [<7.0%]) [24,25]. The addition of insulin detemir (titrated to a mean of 40 units) or insulin degludec (titrated to 51 units) resulted in improvements in glycemic control, with mean end-of-trial HbA_{1c} levels of 54 and 48 mmol/mol (7.1 and 6.5%), respectively. In both cases, there was a low risk of hypoglycemia. The addition of insulin detemir did not reverse the liraglutide-induced weight loss during the run-in period, while initiation and up-titration of insulin degludec resulted in a mean weight gain of 2.0 kg [25].

GLP-1 RA add-on to insulin

In seven Phase III studies, the reverse scenario has been examined, namely the addition of a GLP-1 RA in patients already taking a basal insulin [26–32]. In four studies, the comparison was with placebo, while in the remainder the addition of a GLP-1 RA was compared with insulin intensification using one to three prandial insulin doses. Mathieu *et al.* compared the addition of liraglutide 1.8 mg with insulin aspart (given before the largest meal) in patients with suboptimal HbA_{1c} (≥53 mmol/mol [≥7.0%]) already on insulin degludec and metformin [29]. Liraglutide resulted in a significantly greater reduction in HbA_{1c} versus insulin aspart (8.1 vs 4.3 mmol/mol [-0.74 vs -0.39%]; $p < 0.005$) after the 26-week study period. Liraglutide was also associated with weight loss, while addition of insulin aspart resulted in weight gain (-2.8 vs +0.9 kg; $p < 0.0001$). The observed rate of confirmed hypoglycemia was higher with insulin aspart compared with liraglutide (8.15 vs 1.00 episodes per patient-year; $p < 0.0001$). In contrast, gastrointestinal adverse events were more common with liraglutide, where 1.1% of patients withdrew due to nausea and/or vomiting.

Rosenstock *et al.* compared albiglutide 30 mg once weekly (OW) versus thrice-daily (TID) premeal insulin lispro both given to patients suboptimally controlled by insulin glargine and metformin and/or pioglitazone [30]. Once again, the study lasted for 26 weeks and at study-end, there was a significantly greater reduction in HbA_{1c} seen with albiglutide than with insulin lispro (9 vs 7.3 mmol/mol [-0.82 vs -0.66%]; $p < 0.0001$). Mean weight of subjects decreased with albiglutide but increased with lispro (-0.73 vs +0.81 kg; $p < 0.0001$). More patients experienced documented hypoglycemia with lispro versus albiglutide (30 vs 16%) but there were more gastrointestinal adverse events with albiglutide.

In the third study, Diamant *et al.* compared the premeal addition of exenatide twice-daily versus insulin lispro before three meals to patients uncontrolled on insulin glargine [32]. Exenatide was noninferior to insulin lispro in terms of HbA_{1c} reduction (12.4 vs 12.1 mmol/mol [-1.13 vs -1.10%]) while weight was decreased with exenatide and increased with insulin lispro (-2.5 vs +2.1 kg; $p < 0.001$). Considering minor hypoglycemia, the incidence was significantly greater with lispro (41 vs 30%; $p = 0.004$), while more patients experienced gastrointestinal adverse events with exenatide (47 vs 13%), with 3.5% of patients in this group withdrawing due to nausea and/or vomiting.

To summarize, several clinical trials have shown that combining a GLP-1 RA with basal insulin results in a significant HbA_{1c} reduction, with low risk of hypoglycemia and the potential for weight loss [24–31]. The studies with liraglutide and albiglutide suggest that this can be an attractive alternative to the more complex regime intensification with premeal insulin [29,30]. For these reasons, a product combining liraglutide and insulin degludec in a single, once-daily injection is undergoing a clinical trial program (known

as DUAL). A coformulation of lixisenatide and insulin glargine is also being developed.

A fixed-ratio combination of insulin & a GLP-1 RA

IDegLira is a fixed-ratio combination of basal insulin (insulin degludec) and a GLP-1 RA (liraglutide), administered once-daily from a prefilled pen device. One 'dose-step' of IDegLira contains 1 unit of insulin degludec and 0.036 mg of liraglutide and the pen allows for a maximum dose of 50 units insulin degludec with 1.8 mg liraglutide (in-keeping with the maximum licensed dose of liraglutide for treating T2DM). The starting dose of IDegLira in Phase III trials has been 10 dose-steps (10 units insulin degludec/0.36 mg liraglutide) in patients on oral antidiabetic agents and 16 dose-steps (16 units insulin degludec/0.58 mg liraglutide) in patients previously uncontrolled on basal insulin or a GLP-1 RA. These initial starting levels have been recommended so as to limit the gastrointestinal upset, typically seen when patients are first-exposed to GLP-RAs. The pharmacokinetic properties of the individual components of insulin degludec and liraglutide are preserved and equivalent to the individual formulations [33]. Currently, IDegLira is approved for use in Europe 2014 [34]. However, approval by the FDA for use in the USA is dependent on demonstration of the cardiovascular safety of insulin degludec. The interim results of the DEVOTE study examining this are currently being examined by the FDA with an opinion expected during 2015. Provided these results are favorable then approval for use would be expected for degludec and subsequently IDegLira.

Dose titration

Dose up-titration of insulin in the UK is poor, a further indication of clinical inertia in T2DM management, with many patients remaining on suboptimal doses. For IDegLira, effective outcomes from this combination will only be seen if up-titration is driven in clinical practice and so a simple titration algorithm is essential. In the Phase III trials, titration has been performed in a very similar manner that used in basal insulin studies. This has involved twice-weekly changes, based on the mean of three self-measured fasting plasma glucose (FPG) assessments and has been largely patient-led. The target for FPG in both DUAL I and II studies was 4.0–5.0 mmol/l and dose changes were +2 dose-steps, if patients were above target and -2 dose-steps if below. Although in real-life clinical practice, the fasting targets will be individualized (and probably higher), this algorithm should be simple enough for widespread adoption.

Two Phase III clinical studies of IDegLira have been completed and published: DUAL I (IDegLira vs insulin degludec or liraglutide in patients uncontrolled on OADs; 26 weeks with a 26-week extension) and DUAL II (IDegLira vs insulin degludec in patients uncontrolled on basal insulin + OADs; 26 weeks) [35,36]. These are now described in more detail (also see **Table 2**).

DUAL I

IDegLira was compared with its individual components (insulin degludec and liraglutide) in a randomised, open-label study of 1663 patients with suboptimally controlled T2DM (HbA_{1c} 53–86 mmol/mol [7.0–10.0%]) already taking metformin ± pioglitazone [35]. Liraglutide was titrated by 0.6 mg/week to a maintenance dose of 1.8 mg, as per its summary of product characteristics (SPC); IDegLira could be titrated to a maximum of 50 dose-steps (50 units IDeg/1.8 mg liraglutide); no maximum dose was specified for insulin degludec. More than 80% of patients were receiving metformin monotherapy at baseline with a mean HbA_{1c} of 67 mmol/mol (8.3%). The mean BMI of the study population was 31.2 kg/m^2, their mean age was 55 years and the duration of diabetes was around 7 years. The majority of subjects included were either Caucasian (62%) or Asian (28%).

Treatment with IDegLira resulted in a significantly greater reduction in HbA_{1c} (-1.9%) and lower end-of-trial HbA_{1c} (46 mmol/mol [6.4%]) compared with either component alone (all p-values < 0.0001) **(Figure 1)**. At the end of trial (26 weeks), 81% of patients achieved an HbA_{1c} of <53 mmol/mol (<7.0%) with IDegLira, and this was significantly greater than with insulin degludec (65%) or liraglutide (60%) alone ($p < 0.0001$). Similarly, more patients achieved an HbA_{1c} of ≤48 mmol/mol (≤6.5%), the tighter AACE target, with IDegLira (69.7%) versus insulin degludec (47.5%) and liraglutide (41.1%). At study completion, the mean insulin degludec dose was 28% lower in the IDegLira arm at 38 versus 53 U the degludec arm and the mean liraglutide dose was lower in the IDegLira arm compared with the liraglutide arm, although some patients were at the maximal dose of IDegLira.

Table 2. Summary of key data from the IDegLira Phase IIIa clinical trials.

Study	Study duration (weeks)	Treatment arms (n)	Withdrawn (%)	Mean ΔHbA$_{1c}$ (%)	Mean EOT HbA$_{1c}$(%)	Hypoglycemia (events/patient year)	Mean Δ body weight (kg)	Ref.
DUAL I	26	IDegLira (833)	90 (12%)	-1.9†‡	6.4	1.8†‡	-0.5†‡	[35]
		IDeg (413)	47 (12%)	-1.4	6.9	2.6	+1.6	
		Lira 1.8 mg (414)	71 (18%)	-1.3	7.0	0.2	-3.0	
DUAL I extension	52	IDegLira (833)	5 (0.6%)	-1.8†‡	6.4	1.8†‡	-0.4†‡	[37]
		IDeg (413)	1 (0.2%)	-1.4	6.9	2.8	+2.3	
		Lira 1.8 mg (414)	2 (0.5%)	-1.2	7.1	0.2	-3.0	
DUAL II	26	IDegLira (207)	32 (16%)	-1.9†	6.9	1.5	-2.7†	[36]
		IDeg (max 50 units) (206)	35 (17%)	-0.9	8.0	2.6	0.0	

†p < 0.0001 versus IDeg.
‡p < 0.0001 versus liraglutide.
EOT: End of trial; IDeg: Insulin degludec; IDegLira: Insulin degludec/liraglutide.

The improved glycemic effects of IDegLira compared with its individual components can be explained by a greater reduction in FPG with IDegLira versus liraglutide (-3.6 vs -1.8 mmol/l; p < 0.0001) and the greater reduction in mean postprandial glucose (PPG) increment after all three meals with IDegLira versus insulin degludec (p < 0.0001). The liraglutide component of IDegLira also mitigated the insulin-associated weight gain **(Table 2)**.

The relative risk of hypoglycemia was 32% lower with IDegLira compared with insulin degludec alone (p = 0.0023) but, as would be expected, higher than with liraglutide (p < 0.0001), which had a very low hypoglycemia rate **(Table 2)**. Fewer patients experienced gastrointestinal adverse events with IDegLira compared with liraglutide, and this is likely to be due to the slower up-titration of the liraglutide component in the IDegLira group than is recommended by the SPC for liraglutide given alone. There was also a lower mean end-of-trial dose of liraglutide, which may have contributed to this improved outcome. The lower number of withdrawals seen in the IDegLira and degludec arms of the trial, 12% in each group compared with 18% in the liraglutide arm is attributed to better gastrointestinal tolerability.

DUAL I extension study

In the 26-week extension study of DUAL I, the glycemic outcomes reported in the first study period were maintained for all treatment arms. The dose of insulin in the insulin degludec arm increased by a further nine units from week 26 to 52, while IDegLira maintained the end-of-trial HbA$_{1c}$ of 46 mmol/mol (6.4%) at week 26–52 with only a mean dose increase of 1 dose-step to 39 dose-steps, equivalent to a final dose of 39 units degludec and 1.4 mg liraglutide **(Table 2)**. Although by 52 weeks, 57% of subjects in the IDegLira group had reached the maximum of 50 dose-steps compared with 44% at 26 weeks [37].

DUAL II

DUAL II is a 26-week, double-blind, randomized study which was designed to assess the contribution of the liraglutide component of IDegLira by comparing it with insulin degludec only, the latter having a dose cap of 50 units. The trial included patients with T2DM uncontrolled on basal insulin (20–40 units) in combination with metformin and sulfonylurea/glinides (the latter being discontinued at baseline) [36]. The subjects included had a mean age of 57 years with a mean duration of diabetes of between 10 and 11 years. Over 75% of trial participants were Caucasian.

At the end of study, the mean insulin dose was equivalent for both the IDegLira and insulin degludec arms, allowing for evaluation of the contribution of the liraglutide component of IDegLira **(Table 2)**. HbA$_{1c}$ reduction was 12.1 mmol/mol (1.1%) greater with IDegLira compared with insulin degludec (p < 0.0001) **(Table 2)**, and a higher proportion of patients achieved the HbA$_{1c}$ target of <53 mmol/mol (<7.0%) (60 vs 23%; p < 0.0001). At the end of the study, the mean dose of degludec either alone or as part of IDegLira was the equivalent at 45 U.

The mean reduction of FPG was significantly greater with IDegLira versus insulin degludec (-3.5 vs -2.6 mmol/l; p = 0.0019) and the mean self-measured 9-point glucose profile was also

lower ($p < 0.0001$). Use of IDegLira in patients previously uncontrolled on basal insulin therapy resulted in a mean weight loss of 2.7 kg compared with no change in the insulin degludec group ($p < 0.0001$). The rates of confirmed hypoglycemia were similar with IDegLira and insulin degludec, despite the lower end-of-trial HbA_{1c} in the IDegLira arm **(Table 2)**. Overall, the frequency of adverse events was similar, with very low and comparable rates of nausea, possibly reflecting that this was a double-blind trial (in contrast to all previous insulin vs GLP-1 RA studies).

These data illustrate that in patients with T2DM uncontrolled on basal insulin, the addition of the liraglutide component in IDegLira offers an additional HbA_{1c} reduction to insulin degludec administered at an equivalent insulin dose. This benefit was without a higher risk of hypoglycemia and with the additional bonus of weight loss.

Choosing patients for IDegLira

There have been several *post hoc* analyses of the DUAL I and II studies and these have suggested that the efficacy of IDegLira is independent of both diabetes duration and baseline BMI. Furthermore, IDegLira was effective across the range of baseline HbA_{1c} categories studied [38,39]; for example, in patients with baseline HbA_{1c} >75 mmol/mol (>9.0%), the mean HbA_{1c} reduction was 25.4 mmol/mol (2.5%) in both DUAL I and II, while in DUAL I in patients with a mean HbA_{1c} just above target (≤58 mmol/mol [≤7.5%]), there was still a reduction of 13.2 mmol/mol (1.2%) to a mean end-of-trial HbA_{1c} of 42 mmol/mol (6.0%) [35].

The potential to deliver a significant reduction in HbA_{1c} coupled with less hypoglycemia and potential weight reduction makes the combination of GLP-1 RA and insulin very attractive. The wider economic benefit of less hypoglycemic episodes on the paramedic and acute medical services and lower incidence of long-term complications only increases their appeal. Based on the SPC, IDegLira is licensed for use with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycemic control [34]. Currently, the clinical trial data suggest that IDegLira may be usefully considered in patients who are otherwise being considered for insulin or GLP-1 RA therapy where good glycemic control is a priority and increase in weight a significant concern. Current practice in the UK is typically the addition of injectable GLP-1 agonist therapy or once-daily basal insulin when the combination of up to three oral agents has failed to deliver satisfactory blood glucose control. Should escalation beyond this stage be required, usually this would involve combination of insulin and GLP-1 RA. This combination is associated with superior HbA_{1c} lowering, less weight gain and a lower incidence of hypoglycemia when compared with a basal plus or basal bolus regimes (24–30). Therefore, it seems the patients who should be considered

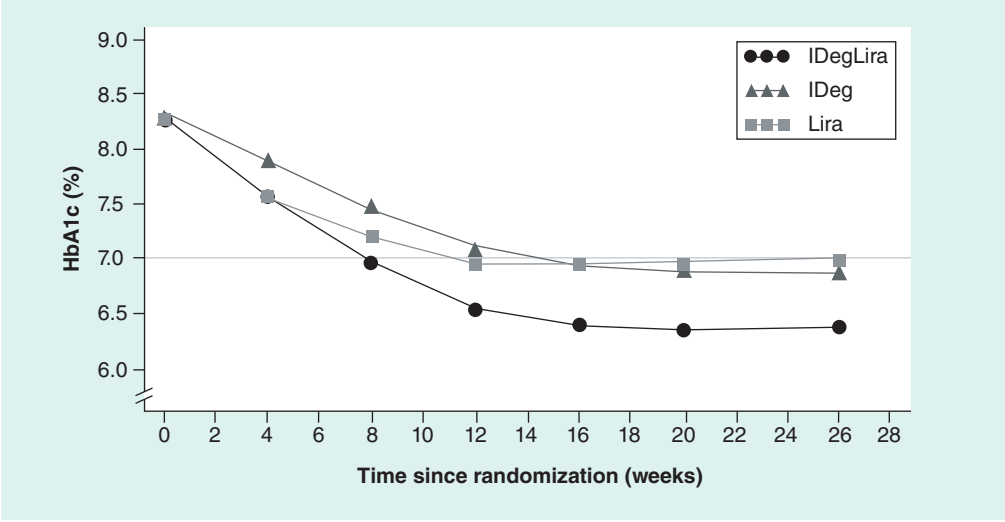

Figure 1. Mean *HbA1c* over 26 weeks according to treatment arm.
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for treatment with IDegLira are those being considered for a combination of basal insulin and GLP-1R. The decision would then be whether to give two separate injections or a premixed combination therapy. Factors that will influence this decision would include the degree of HbA_{1c} lowering required, the risk of hypoglycemia, concern about weight gain, issues of tolerability and the costs of therapy. The group of patients most likely to benefit from IDegLira are those with significant weight problems, already receiving basal insulin and who are failing to achieve their HbA_{1c} target. Although not studied to date, the improved gastrointestinal tolerability of IDegLira versus a stand-alone GLP-1 RA may make it a possible option in patients who have previously been unable to tolerate GLP–1 RA up-titration.

Given that IDegLira involves the combination of relatively expensive glucose-lowering medications, careful consideration must be given to where it is positioned in the treatment pathway for T2DM. On a positive note, the cost of IDegLira is lower than the combined cost of the individual components insulin degludec and liraglutide 1.8 mg. However, currently the NICE recommendation is to use a maximal dose of 1.2 mg rather than 1.8 mg of liraglutide. Although, on occasion, responders have the dose of liraglutide increased to 1.8 mg daily. Therefore, the average dose of liraglutide in the UK lies somewhere between 1.2 and 1.8 mg daily. The cost of IDegLira is similar to the combined price of a traditional basal analog insulin such as Lantus or Levemir and 1.8 mg of liraglutide. Interestingly, the average dose of liraglutide use in the fixed combination of IDegLira in DUAL 1 was 1.4 mg [35]. We must also remember that the greatest costs of diabetes arise from managing the associated complications, which can be attenuated by optimal glycemic control.

Ongoing trials

There will be more clinical trial data for IDegLira from the DUAL program, some of which are expected in the later part of 2015. These studies are investigating the safety and efficacy of IDegLira when added to preexisting sulfonylurea ± metformin therapy (the DUAL IV study) and assessing the switch from a GLP-1 RA (DUAL III). Although IDegLira is the only licensed fixed-ratio combination of a GLP-1 RA and basal insulin, there is another combination under development, known as 'LixiLan'. LixiLan combines lixisenatide and insulin glargine (trade-name 'Lantus', hence the name) in a single pen device, which in the Phase II clinical trials had a maximum dose of 30 μg lixisenatide and 60 U insulin glargine. Two LixiLan Phase III studies were initiated in 2014 and have now fully recruited.

Conclusion

Insulin initiation and intensification are delayed in the management of T2DM, especially in the UK and this is partly due to the association with weight gain and hypoglycemia. This exposes patients to increased risk of complications and increases the economic burden of T2DM. Intensification of insulin therapy to improve glycemic control typically results in further weight gain and increased risk of hypoglycemia, particularly as patients approach target HbA_{1c}. Use of an SGLT-2 inhibitor, DPP-4 inhibitor or GLP-1 RA in combination with basal insulin can reduce these insulin-associated consequences. Combining liraglutide and insulin degludec in a once-daily, fixed-ratio injection, as an add-on to oral antidiabetic therapy or basal insulin, can offer substantial lowering of HbA_{1c} without increasing hypoglycemia (vs basal insulin alone) and with no mean weight increase. Furthermore, the levels of achieved HbA_{1c} in the initial clinical trials are better than have been seen with any previous glucose-lowering therapies. Additional data from the DUAL and LixiLan clinical programs are awaited to firmly establish the safety and efficacy of fixed-ratio combinations in additional patient populations with T2DM.

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References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of Type 2 diabetes mellitus. *Diabetes* 58(4), 773–795 (2009).

2 Dagogo-Jack S, Santiago JV. Pathophysiology of Type 2 diabetes and modes of action of therapeutic interventions. *Arch. Intern. Med.* 157(16), 1802–1817 (1997).

3 Inzucchi SE, Bergenstal RM, Buse JB *et al.* Management of hyperglycemia in Type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 55, 1577–1596 (2012).

4 NICE. Type 2 diabetes: newer agents for blood glucose control in Type 2 diabetes. www.nice.org.uk/guidance/cg87/resources/cg87-type-2-diabetes-newer-agents-a-partial-update-of-cg66-short-guideline2

5 Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with Type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care* 36, 3411–3417 (2013).

• **Highlights the clinical inertia among clinicians in the UK when making decisions about escalation of antidiabetic therapy.**

6 Blak BT, Smith HT, Hards M, Curtis BH, Ivanyi T. Optimization of insulin therapy in patients with Type 2 diabetes mellitus: beyond basal insulin. *Diabet. Med.* 26, e13–e20 (2012).

7 Khunti K, Damci T, Meneghini L, Pan CY, Yale JF, SOLVE Study Group. Study of once-daily Levemir (SOLVE™): insights into the timing of insulin initiation in people with poorly controlled Type 2 diabetes in routine clinical practice. *Diabetes Obes. Metab.* 14, 654–661 (2012).

8 Peyrot M, Rubin RR, Lauritzen T *et al.* Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* (11), 2673–2679 (2005).

9 Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated Type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* 131, 182–188 (1999).

10 Swinnen SG, Dain MP, Mauricio D, DeVries JH, Hoekstra JB, Holleman F. Continuation versus discontinuation of insulin secretagogues when initiating insulin in Type 2 diabetes. *Diabetes Obes. Metab.* 12, 923–925 (2010).

11 Bristol Myers Squibb-AstraZeneca. Summary of product characteristics, Forxiga 5 mg and 10 mg. www.medicines.org.uk/emc/medicine/27188/SPC/Forxiga+5+mg++%26+10+mg+film+coated+tablets/

12 Janssen-Cilag Ltd. Summary of product characteristics, Invokana 100 mg. www.medicines.org.uk/emc/medicine/28400

13 Boehringer Ingelheim Limited. Summary of product characteristics, Jardiance 25 mg. www.medicines.org.uk/emc/medicine/28974

14 Rosenstock J, Jelaska A, Frappin G *et al.* Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled Type 2 diabetes. *Diabetes Care* 37, 1815–1823 (2014).

15 Matthews DR, Fulcher G, Perkovic V *et al.* Efficacy and safety of canagliflozin (CANA), an inhibitor of sodium glucose co-transporter 2 (SGLT2), added-on to insulin therapy +/– oral agents in Type 2 diabetes. *Diabetologia* 55(Suppl. 1), S314 (Abstract 764) (2012).

16 Wilding JP, Woo V, Soler NG *et al.* Long-term efficacy of dapagliflozin in patients with Type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann. Intern. Med.* 156, 405–415 (2012).

17 Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with Type 2 diabetes reduces HbA_{1C} without causing weight gain or increased hypoglycemia. *Diabetes Obes. Metab.* 11, 1145–1152 (2009).

18 Vilsbøll T, Rosenstock J, Yki-Järvinen H *et al.* Efficacy and safety of sitagliptin when added to insulin therapy in patients with Type 2 diabetes. *Diabetes Obes. Metab.* 12, 167–177 (2010).

19 Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled Type 2 diabetes on insulin alone or insulin combined with metformin. *Curr. Med. Res. Opin.* 28, 513–523 (2012).

20 Yki-Järvinen H, Rosenstock J, Durán-Garcia S *et al.* Effects of adding linagliptin to basal insulin regimen for inadequately controlled Type 2 diabetes: a ≥52-week randomized, double-blind study. *Diabetes Care* 36, 3875–3881 (2013).

21 Kothny W, Foley J, Kozlovski P, Shao Q, Gallwitz B, Lukashevich V. Improved glycemic control with vildagliptin added to insulin, with or without metformin, in patients with Type 2 diabetes mellitus. *Diabetes Obes. Metab.* 15, 252–257 (2013).

22 Thong KY, Jose B, Sukumar N *et al.* Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit. *Diabetes Obes. Metab.* 13, 703–720 (2011).

• **Illustrates prescribing habits in the UK with regards to use of GLP-1 RA.**

23 Thong KY, Gupta PS, Cull ML *et al.* GLP–1 receptor agonists in Type 2 diabetes – NICE guidelines versus clinical practice. *Br. J. Diabetes Vasc. Dis.* 14, 52–59 (2014).

24 DeVries JH, Bain SC, Rodbard HW *et al.* Sequential intensification of metformin treatment in Type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care* 35, 1446–1454 (2012).

25 Aroda VR, Bailey T, Cariou B *et al.* The effect of insulin degludec in combination with liraglutide and metformin in patients with Type 2 diabetes requiring treatment intensification. *Diabetologia* 57(Suppl. 1), S68, Abstract 145 (2014).

26 Buse JB, Bergenstal RM, Glass LC *et al.* Use of twice-daily exenatide in basal insulin-treated patients with Type 2 diabetes: a randomized, controlled trial. *Ann. Intern. Med.* 154, 103–112 (2011).

27 Riddle MC, Aronson R, Home P *et al.* Adding once-daily lixisenatide for Type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care* 36, 2489–2496 (2013).

28 Riddle MC, Forst T, Aronson R *et al.* Adding once-daily lixisenatide for Type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulinglargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes Care* 36, 2497–2503 (2013).

29 Mathieu C, Rodbard HW, Cariou B *et al.* A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with Type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes. Metab.* 16, 636–644 (2014).

• **Demonstrates the effectiveness of a combination of GLP-1 RA compared with additional insulin injection in patients with Type 2 diabetes.**

30 Rosenstock J, Fonseca VA, Gross JL *et al.* Advancing basal insulin replacement in

Type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor a gonist, versus thrice-daily prandial insulin lispro. *Diabetes Care* 37, 2317–2325 (2014).

31 Ahmann AJ, Rodbard HW, Rosenstock J *et al.* Efficacy and safety of liraglutide versus placebo when added to basal insulin analogs in patients with Type 2 diabetes (LIRA-ADD2BASAL). *Diabetes* 63 (Suppl. 1), A87, Abstract 331-OR (2014).

32 Diamant M, Nauck MA, Shaginian R *et al.* Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in Type 2 diabetes. *Diabetes Care* 37, 2763–2673 (2014).

33 Kapitza C, Bode B, Ingwersen SH, Jacobsen LV, Poulsen P. Preserved pharmacokinetic exposure and distinct glycemic effects of insulin degludec and liraglutide in IDegLira, a fixed-ratio combination therapy. *J. Clin. Pharmacol.* doi:10.1002/jcph.549 (2015) (Epub ahead of print).

34 IDegLira SmPC. Summary of product characteristics. http://ec.europa.eu/health/documents/community-register/2014/20140918129550/anx_129550_en.pdf

35 Gough SC, Bode B, Woo V *et al.* Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a Phase 3, open-label, randomized, 26-week, treat-to-target trial in insulin-naive patients with Type 2 diabetes. *Lancet Diabetes Endocrinol.* 2, 885–893 (2014).

•• **Illustrates the effectiveness of IDegLira in terms of glycemic response, body weight and hypoglycemia in comparison to its individual components.**

36 Buse JB, Vilsbøll T, Thurman J *et al.* Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care* 37, 2926–2933 (2014).

•• **Illustrates the contribution of liraglutide in the fixed combination preparation with insulin degludec.**

37 Gough SCL, Buse JB, Woo VC *et al.* One-year efficacy and safety of IDegLira in patients with Type 2 diabetes. *Diabetes* 63 (Suppl. 1), A17, Abstract 65-OR (2014).

38 Rodbard HW, Buse JB, Woo VC *et al.* IDegLira is efficacious across the range of disease progression in Type 2 diabetes (T2D). *Diabetes* 63 (Suppl. 1), A18, Abstract 67-OR (2014).

39 Buse JB, Rodbard HW, Woo VC *et al.* Impact of BMI on HbA_{1c} reduction, hypoglycemia rates and insulin requirements in response to IDegLira in patients with Type 2 diabetes (T2D). *Diabetes* 63 (Suppl. 1), A18, Abstract 66-OR (2014).